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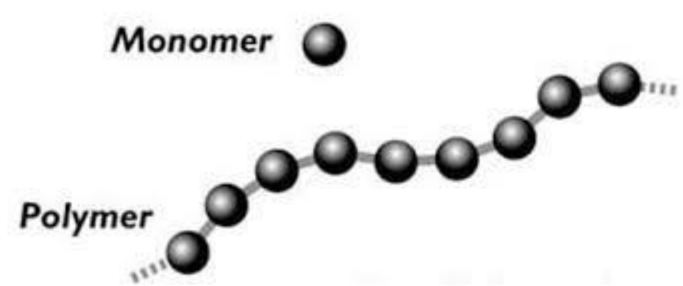
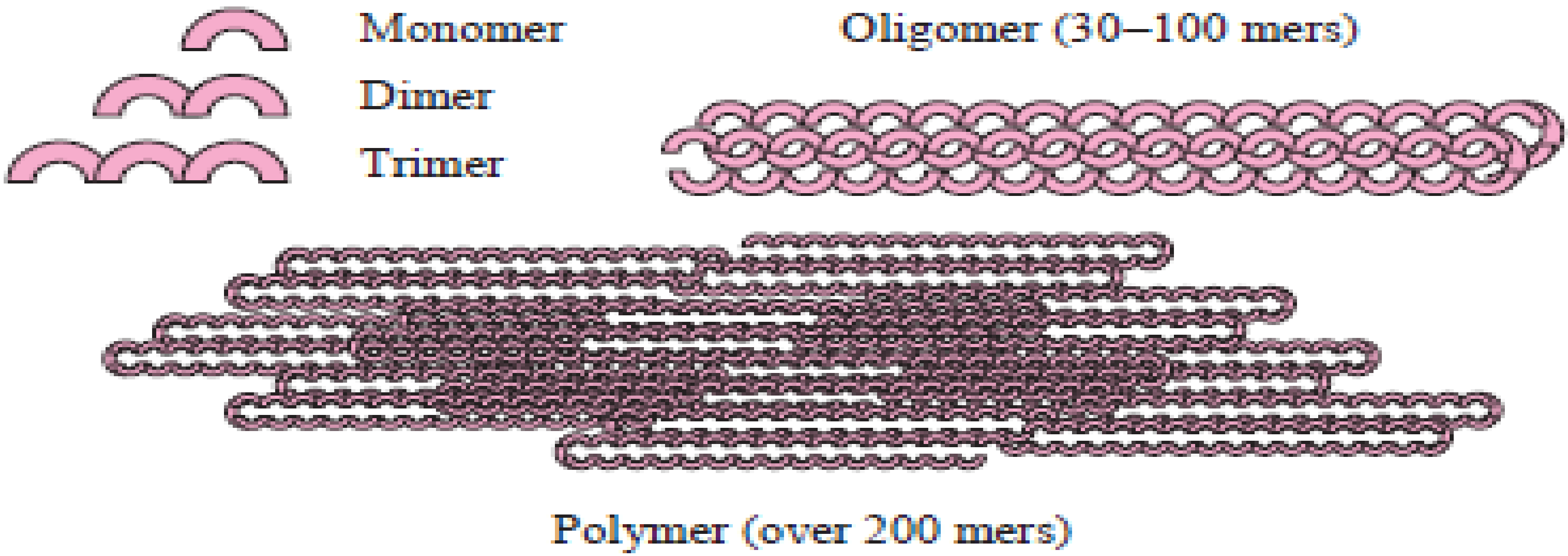
Pharmaceutical Polymers

Polymers in General

- 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.
- "n" number that shows how many monomers are participating in the reaction.
- 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





Degree of Polymerization (DP) = Number of monomers in a chain

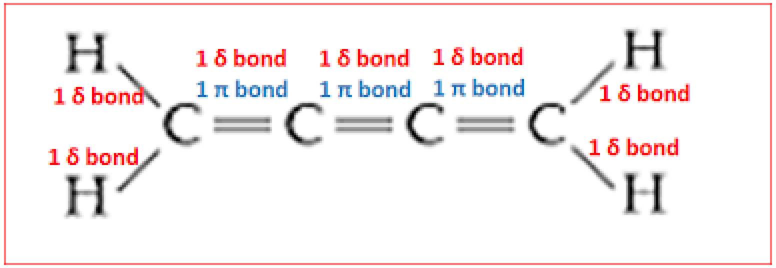
Example

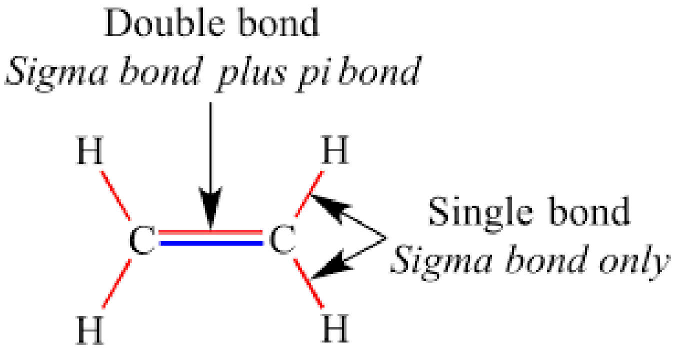
Molecular Weight

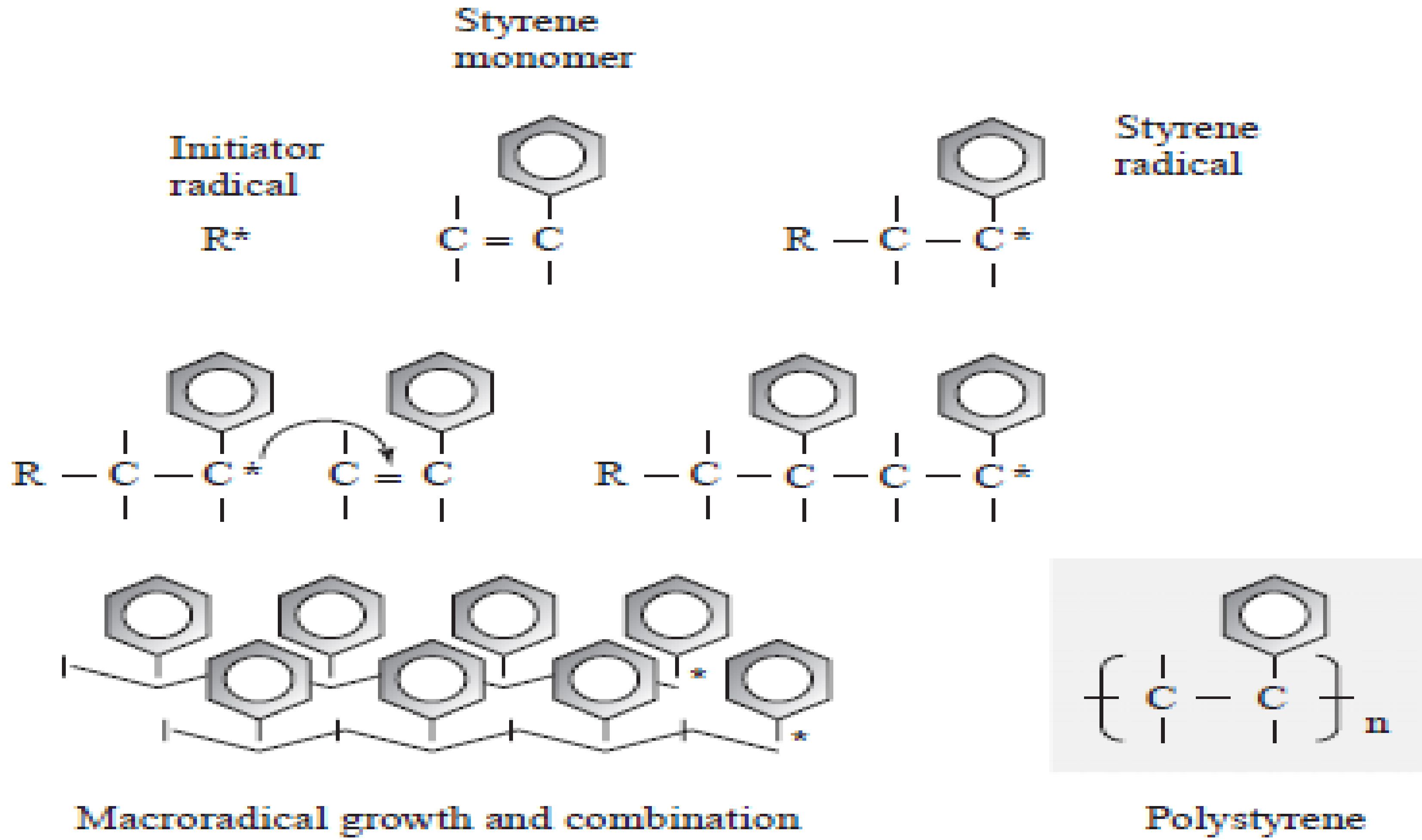
A polyethylene with molecular weight of 100,000 g/mol is made of almost 3570 monomer units (CH_2CH_2) with the molecular weight of 28 g/mol.

Polymer Synthesis

- ✓ To make polymers, monomers have to interact with each other.
- ✓ The structure of the monomer molecule will tell us how we should polymerize it.
- ✓ A monomer may be unsaturated; in other words it may contain a double bond of σ(sigma) and π (pi) between a pair of electrons. The π bond generally requires low energy to break; therefore, polymerization starts at this site by the addition of a free radical on the monomer. On the other hand, if a monomer does not contain a double bond but possesses functional groups such as hydroxyl, carboxyl, or amines, they can interact via condensation.





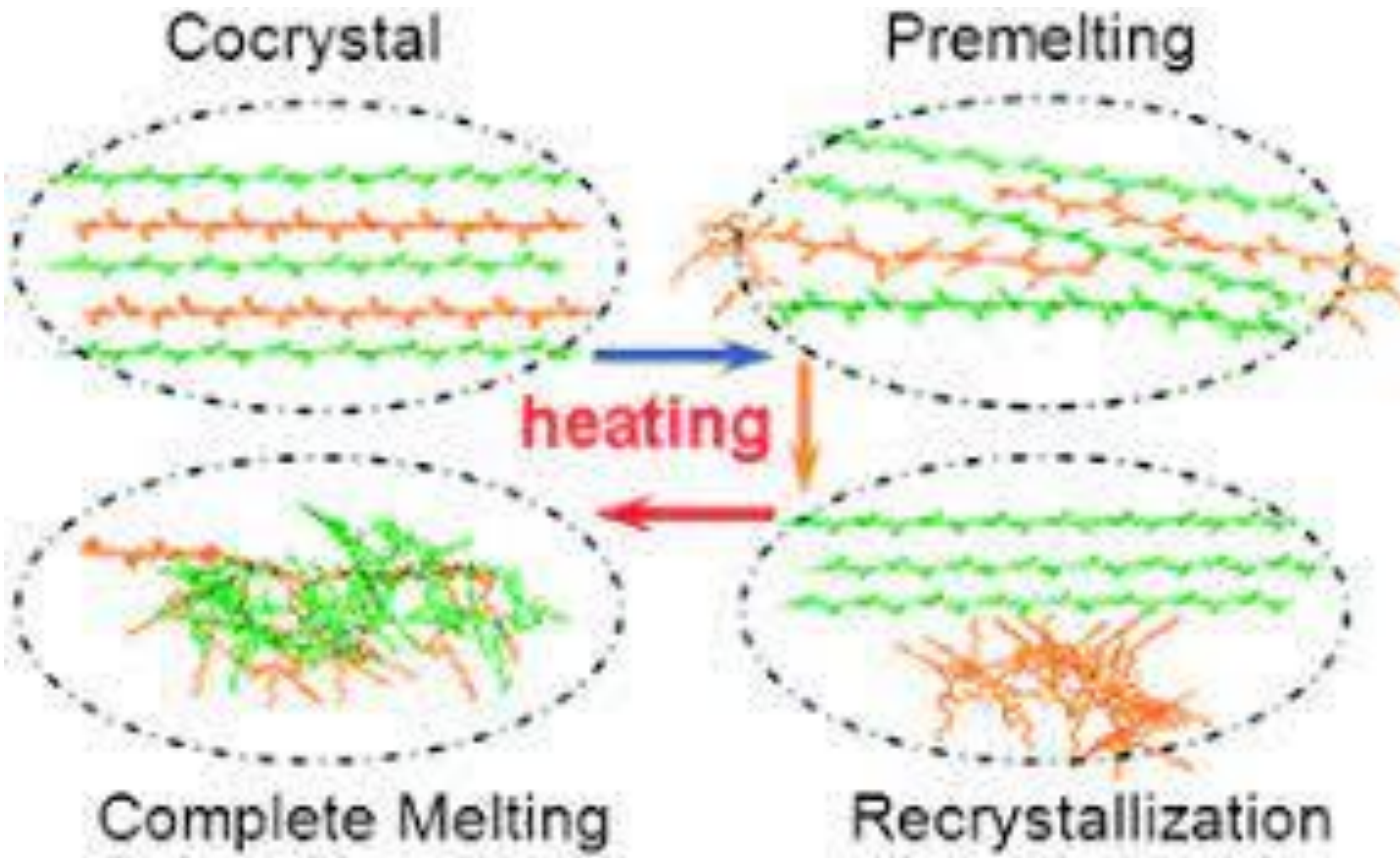

Styrene
monomer
Initiator
radical
R*
Styrene
radical
Macroradical growth and combination
Polystyrene

$NH_2 - R - NH_2$ $HOOC - R' - COOH$	$(- R - NHCO - R' - NHCO -)$ Polyamide
$HO - R - OH$ $O = C = N - R' - N = C = O$	$(- NHCOO - R - NHCOO - R' -)$ Polyurethane
$HO - R - OH$ $HOOC - R' - COOH$	$(- R - COO - R' - COO -)$ Polyester

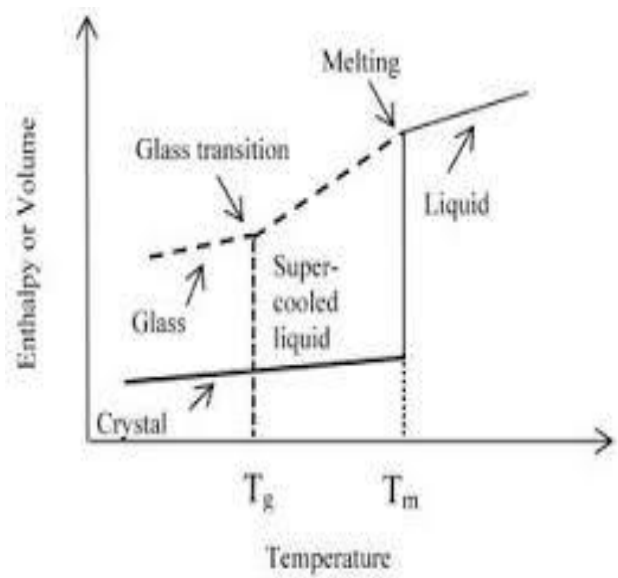
Polymer Properties

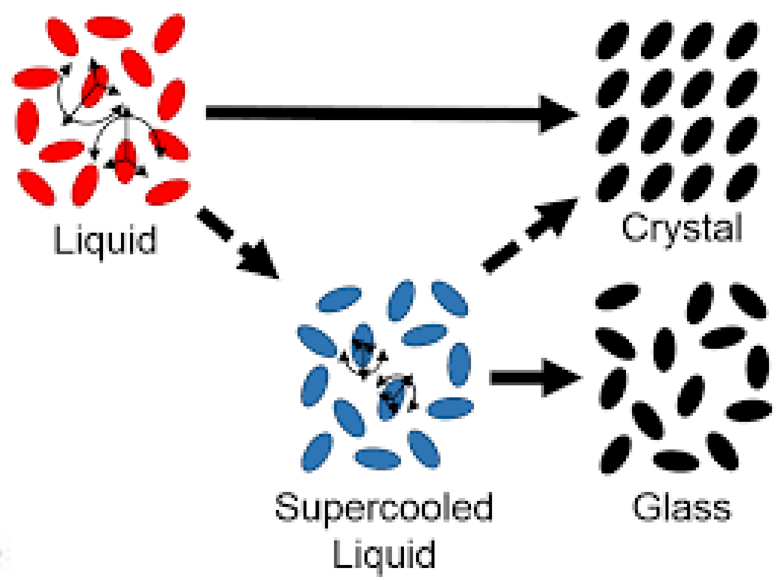
Crystalline and Amorphous Polymers

Polymers display different thermal, physical, and mechanical properties depending on their structure, molecular weight, linearity, intra- and intermolecular interactions. If the structure is linear, polymer chains can pack together in regular arrays. For example, polypropylene chains fit together in a way that intermolecular attractions stabilize the chains into a regular lattice or crystalline state. With increased temperature, the crystal cells (crystallites) start to melt and the whole polymer mass suddenly melts at a certain temperature. Above the melting temperature, polymer molecules are in continuous motion and the molecules can slip past one another.


Cocrystal
Premelting
heating
Complete Melting
Recrystallization

In many cases, the structure of a polymer is so irregular that crystal formation is thermodynamically infeasible. Such polymers form glass instead of crystal domains. A glass is a solid material existing in a noncrystalline (i.e., amorphous) state. the polymer molecules forcedly adopt a disordered state and form an amorphous structure. Amorphous or glassy polymers do not generally display a sharp melting point; instead, they soften over a wide temperature range





Polymer strength and stiffness increases with crystallinity as a result of increased intermolecular interactions. With an increase in crystallinity, the optical properties of a polymer are changed from transparent (amorphous) to opaque (semicrystalline).

Crystallinity increases the barrier properties of the polymer. Small molecules like drugs or solvents usually cannot penetrate or diffuse through crystalline domains. Diffusion and solubility are two important terms that are related to the level of crystallinity in a polymer. On the other hand, a less crystalline or an amorphous polymer is preferred when the release of a drug or an active material is intended

Example

Crystalline and Amorphous

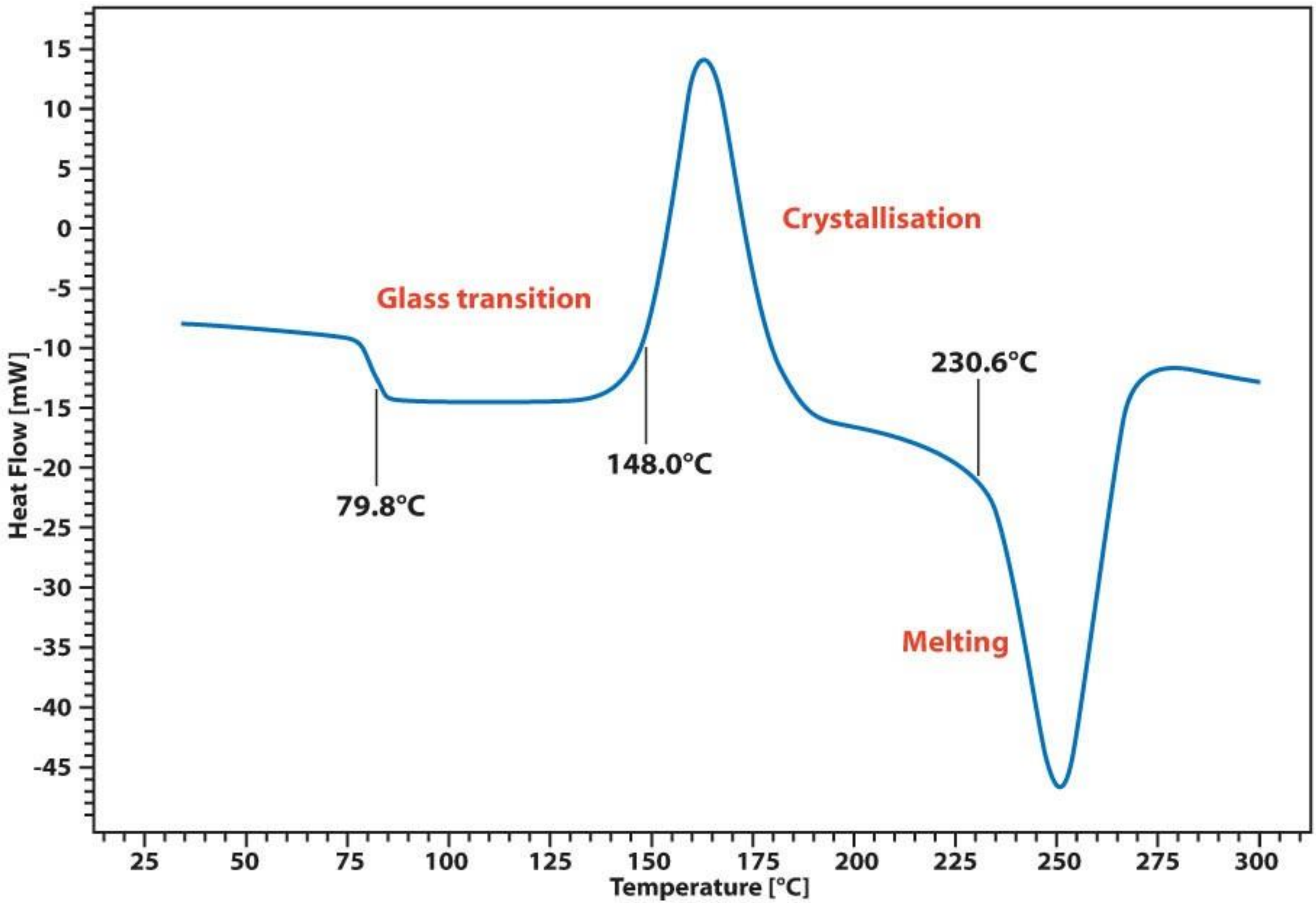
Polystyrene and poly (vinyl acetate) are amorphous with melting range of 35 °C to 85 °C and 70°Cto 115 °C, respectively. On the other hand, poly (butylene terephthalate) and poly (ethylene terephthalate) are very crystalline with sharp melting range of 220 and 250 °C to 260°C, respectively.

poly vinyl acetate

Polystyrene

Thermal Transitions

When a crystal melts, the polymer volume increases significantly as the solid turns to a liquid. The melting temperature (Tm) represents a **first-order thermal** transition in polymers. On the other hand, the volume of an amorphous polymer gradually changes over a wide temperature range or so called glass transition temperature. This behavior represents a **second-order thermal** transition in polymers., Tm and Tg of a given polymer can be detected by **differential scanning calorimetry** (DSC) as an endothermic peak and a baseline shift, respectively .These two thermal transitions reflect the structural movement of the crystalline and amorphous regions of a polymer chain.



Heat Flow [mW]
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
Glass transition
Crystallisation
Melting
79.8°C
148.0°C
230.6°C
25
50
75
100
125
150
175
200
225
250
275
300
Temperature [°C]

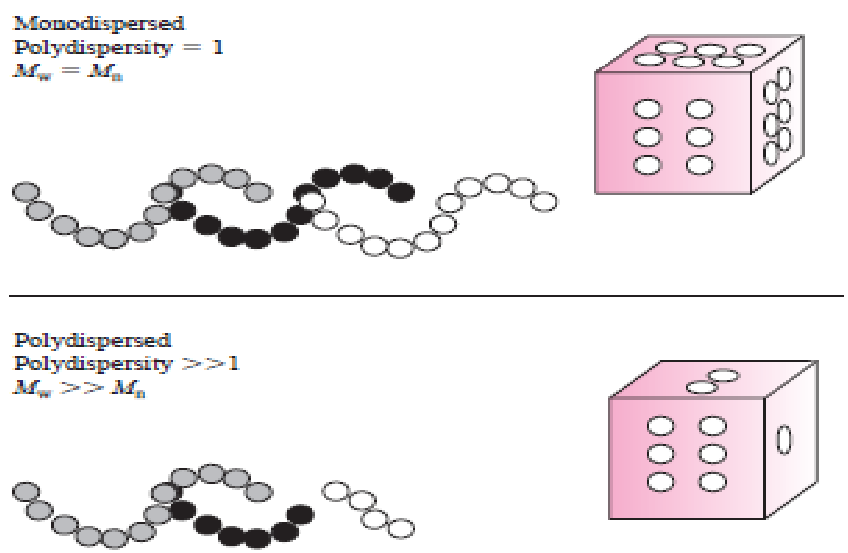
Molecular Weight

Monomers may or may not be added equally to the growing macroradicals . As a result, a polymer batch may contain polymer chains with different lengths (molecular weights) and hence different molecular weight distributions. In general, a given polymer cannot be identified as a molecule with a specific molecular weigh.

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. However, the two most common ways are number M(n) and weight M(w) average calculations

If all polymer chains are **similar** in size, then the number and weight average values will be equivalent. If chains are of **different** sizes, then weight average is distancing itself from the number average value. The term **polydispersity** (PD) indicates how far the weight average can distance itself from the number average. A PD value closer to 1 means the polymer system is close to monodispersed and all of the polymer chains are almost similar in size. The farther the value from 1 indicates that the polymer system is polydispersed and chains are different in size. Consider that you have received two different batches of a same polymer as **The first** batch contains 2 chains of 50,000 g/mol and 10 chains of 20,000 g/mol in size. **The second** batch contains 2 chains of 100,000 g/mol and 10 chains of 10,000 g/mol in size. Calculations show both batches have the same number averages of 25,000 g/mol. the weight average values for the two batches. Surprisingly, two very different numbers, 30,000 g/mol and 70,000 g/mol, are found for the batch 1 and the batch 2, respectively

This shows that the two batches are beyond a doubt different. PD which is the ratio of weight to number averages . Polydispersity of 2.8 versus 1.2 indicates that the batch 2 contains very different chains. If both polymer batches are soluble in water, they will definitely show different solubility behavior in the presence of water. The shorter chains are dissolved faster in water than longer chains. Drug release from these batches will certainly be different as they assume different PD values.



AVERAGE MOLECULAR WEIGHTS AND POLYDISPERSITY

Number of Chains	Batch 1	Batch 2
2	50,000 g/mol	100,000 g/mol
10	20,000 g/mol	10,000 g/mol

Batch 1			Batch 2		
M_n	M_w	PD	M_n	M_w	PD
25,000 g/mol	30,000 g/mol	1.2	25,000 g/mol	70,000 g/mol	2.8

$$\overline{M_n} = \frac{\sum M_i N_i}{N_i} = \frac{(M_1 N_1) + (M_2 N_2) + (M_3 N_3) + (M_4 N_4) + \cdots}{N_1 + N_2 + N_3 + N_4 + \cdots}$$

$$\overline{M_w} = \frac{\sum M_i^2 N_i}{\sum M_i N_i} = \frac{(M_1^2 N_1) + (M_2^2 N_2) + (M_3^2 N_3) + (M_4^2 N_4) + \cdots}{(M_1 N_1) + (M_2 N_2) + (M_3 N_3) + (M_4 N_4) + \cdots}$$

Mechanical properties of a given polymer generally increase with an increase in molecular weight .

In case of water as a solvent, the more hydrophilic polymer will be better. On the other hand, a more lipophilic polymer would be more desirable when the dissolution or swelling medium is organic.

Because of their hydrophilicity and high molecular weight, gums are the candidate of choice for increasing the viscosity of the aqueous solutions or dispersions.

Polymers for Pharmaceutical Applications In a traditional pharmaceutics area, such as tablet manufacturing, polymers are used as tablet **binders** to bind the excipients of the tablet. Modern or advanced pharmaceutical dosage forms utilize polymers for drug **protection**, **taste masking**, **controlled release of a given drug**, **targeted delivery**, **increase drug bioavailability**, and so on and so forth.

polymers have found application in liquid dosage forms as **rheology modifiers**. They are used to **control the viscosity** of an aqueous solution or to **stabilize** suspensions or even for the **granulation** step in preparation of solid dosage forms. Major application of polymers in current pharmaceutical field is for <u>controlled drug release</u>. From the solubility standpoint, pharmaceutical polymers can be classified as <u>**water-soluble and water insoluble**</u> (oil-soluble or organic soluble). The cellulose ethers with methyl and hydroxypropyl substitutions are water-soluble, whereas ethyl cellulose and a group of cellulose esters such as cellulose acetate butyrate or phthalate are organic soluble. Hydrocolloid gums are also used when solubility in water is desirable

Polymers in Pharmaceutical and Biomedical Applications

- **Water-Soluble Synthetic Polymers :**

Poly (acrylic acid), Poly (ethylene glycol).

- **Cellulose-Based Polymers**:

Ethyl cellulose, carboxymethyl cellulose

- **Hydrocolloids:**

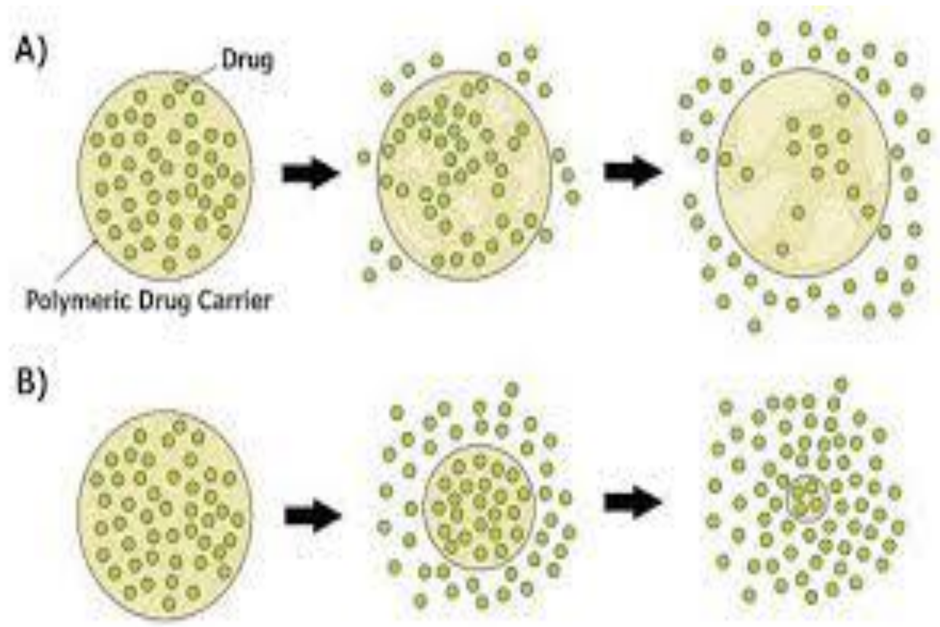
Alginic acid, carageenan

- **Water- Insoluble Biodegradable Polymers :**

(Lactide-co-glycolide) polymers

- **Starch-Based Polymers:**

  Starch, sodium starch glycolate



Polymers in Drug Delivery

Pharmaceutical polymers are widely used to achieve :

- ✓ taste masking;
- ✓ controlled release (e.g., extended, pulsatile, and targeted),
- ✓ enhanced stability,
- ✓ and improved bioavailability

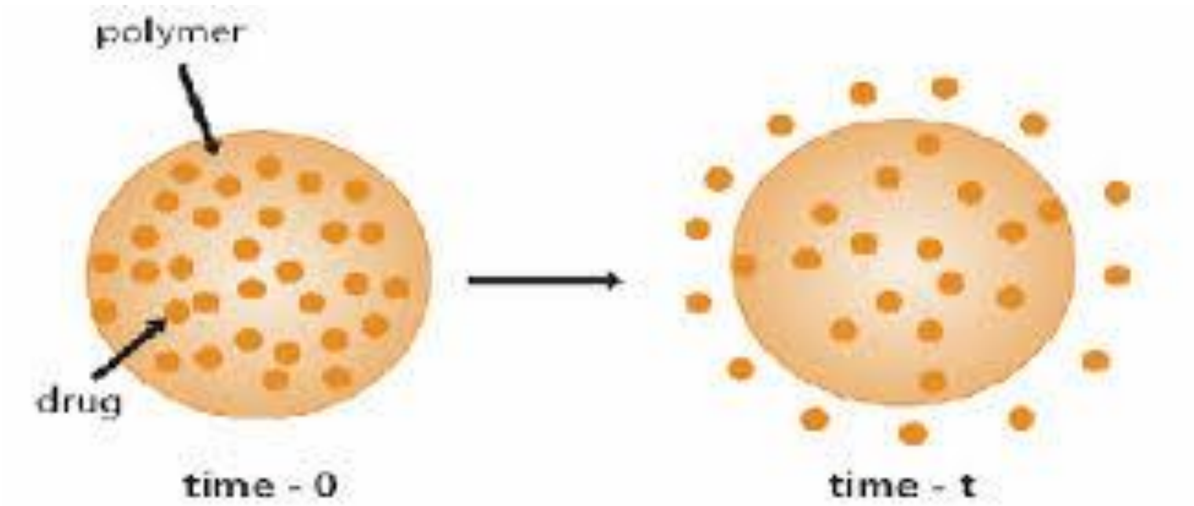
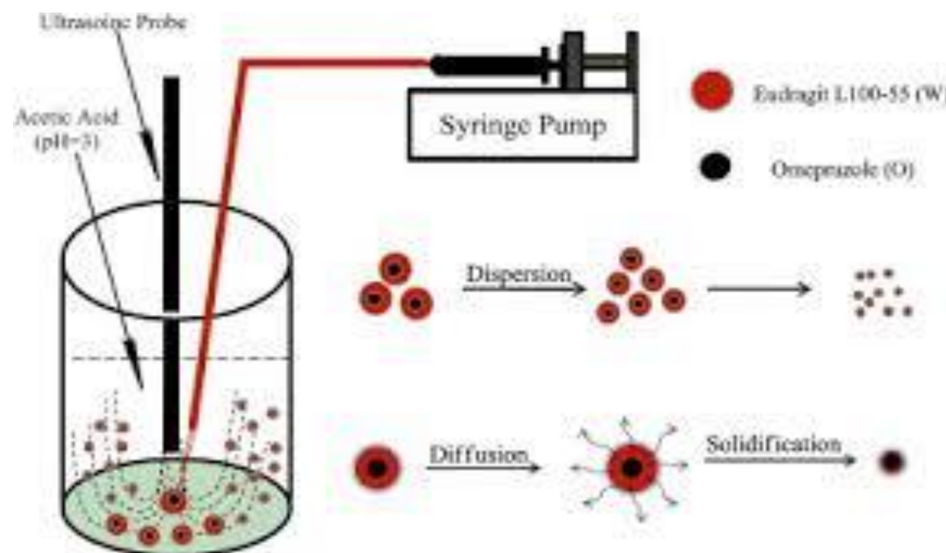


Figure 4. Example for Controlled Drug Delivery (CDD)

Enteric coating

Anionic polymers: Anionic polymers have methacrylic acid as a functional group and are generally used for drug delivery past the stomach into the duodenum, jejunum, ileum, or colon. the pH of the fasted stomach is below pH 3 in nearly every healthy person and below pH 2 in most people, the stomach represents a harsh environment for many drugs. Since the methacrylic group dissociates at the higher pH of the small intestine and colon, anionic polymers such as Eudragit L 100-55 (with dissolution at pH 5.5) and Eudragit S 100 (with dissolution at pH >7.0) are highly desirable




THANK YOU