Drug Delivery Principles and Engineering
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Lecture - 04
Polymers Synthesis

Hello everyone, welcome to another lecture for Drug Delivery Principles and Engineering. Just a quick recap on what we have done so far. So, previously we had learned about what is drug delivery, how are the drugs distributed in the body, so (Refer Time: 00:43) pharmacokinetics.

Now, this was followed by little bit of discussion on prodrugs as well as some polymers. So, we are going to just quickly recap on what we did in the last class in particular. So, we talked about prodrugs, nearly 10 percent of all the drugs in the market are prodrugs.

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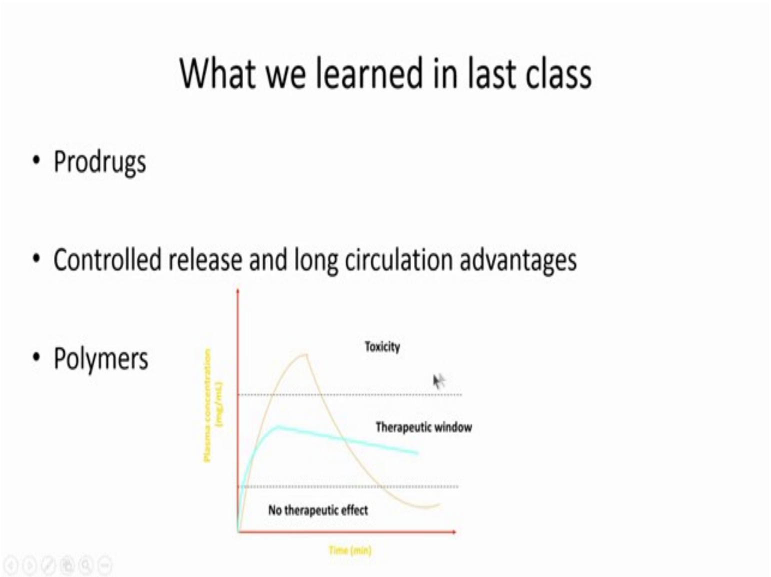

What we learned in last class

- Prodrugs
- Controlled release and long circulation advantages
- Polymers

We also talked about controlled release and long circulation advantages. So, why would you want the drugs to be prolonged and release in the body. So, essentially instead of having a traditional drug delivery system where you have to give high dose, so that it reaches toxicity and then comes down we want more to be stable in this therapeutic window. And then finally, we talked about a little bit about what polymers are and what are the different types in all and we are going to continue our discussion on polymers today.

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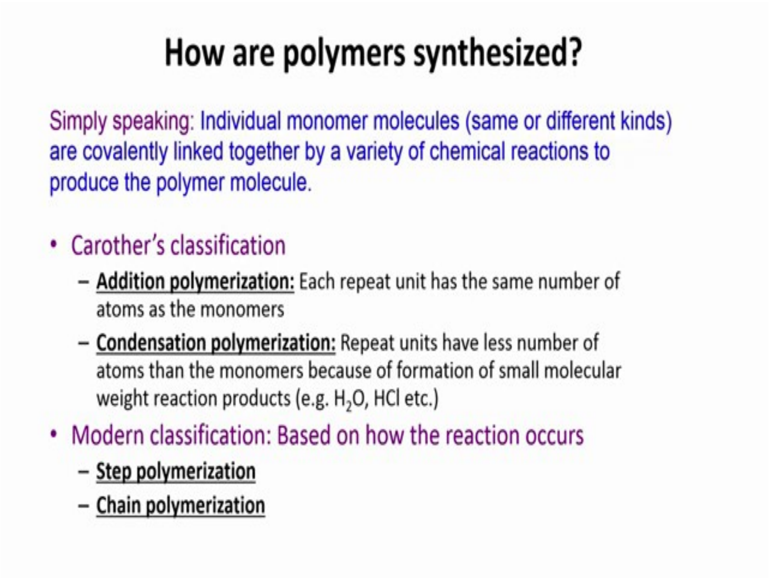

How are polymers synthesized?

Simply speaking: Individual monomer molecules (same or different kinds) are covalently linked together by a variety of chemical reactions to produce the polymer molecule.

- Carother's classification
  - **Addition polymerization:** Each repeat unit has the same number of atoms as the monomers
  - **Condensation polymerization:** Repeat units have less number of atoms than the monomers because of formation of small molecular weight reaction products (e.g. H_2O, HCl etc.)
- Modern classification: Based on how the reaction occurs
  - **Step polymerization**
  - **Chain polymerization**

So, first of all how are polymers synthesized? So, simply speaking its essentially individual monomer molecules come together and are covalently linked by various chemical reactions to produce variety of polymer molecules. So, this is a very simple definition there. So, essentially bringing in monomers and combining them chemically to get different polymers.

Their various classifications in way in which the polymers are synthesized. A traditional classification that has been known in the literature is Carothers classification and it is subdivided into two different types of polymerization one is addition another is condensation. In addition polymerization you essentially have each repeat unit has the same number of atoms as the monomers.

So, essentially they add without releasing any other molecule that is not the part of the polymer, how when condensation polymerizations you have less number of atoms in the polymer, then the individual monomers because typically the reactions involve release of water or acid or something else as a reaction product. This is again as I said Carother is a very traditional classification and on the modern classification is based on how the reaction occurs.

So, in this way it is again subdivided into two different classification when is step polymerization and another is chain polymerization. So, we are going to talk about both of them as we go along in these slides.

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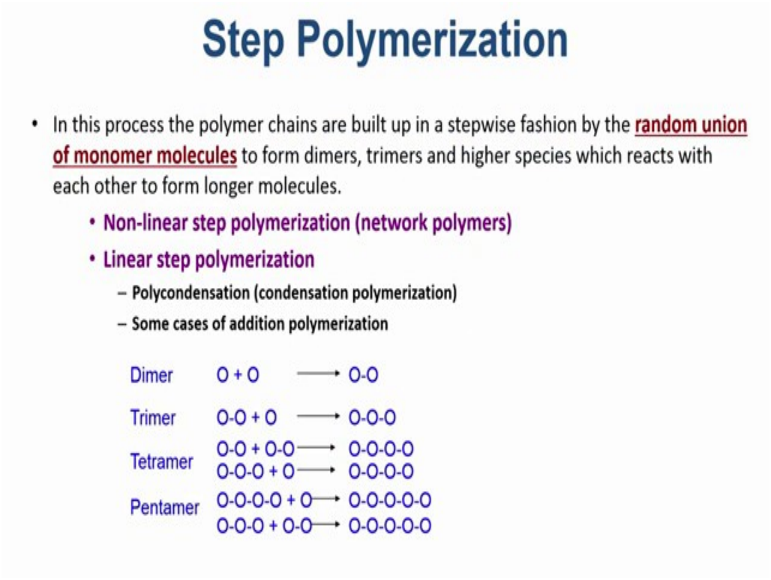

Step Polymerization

- In this process the polymer chains are built up in a stepwise fashion by the **random union of monomer molecules** to form dimers, trimers and higher species which reacts with each other to form longer molecules.
    - **Non-linear step polymerization (network polymers)**
    - **Linear step polymerization**
        - **Polycondensation (condensation polymerization)**
        - **Some cases of addition polymerization**

Dimer O + O → O-O

Trimer O-O + O → O-O-O

Tetramer O-O + O-O → O-O-O-O
O-O-O + O → O-O-O-O

Pentamer O-O-O-O + O → O-O-O-O-O
O-O-O + O-O → O-O-O-O-O

So, talking about step polymerization in this in this process the polymer chains are essentially build up in a stepwise fashion and this could be the random union of individual monomer molecules. So, essentially if we look at reaction here, so you have a dimer being formed by combining of two monomers. A trimer is form again by combining of a dimer to a monomer, but then from there on forward there are several ways that this can happen. So, a tetramer can form either by combining to dimers or by combining a trimer with a monomer and similarly the possibilities increased further as you go along.

So, it is essentially just a random union of monomer molecules which are combining, you can get a linear polymerization this could include both the poly condensation or the addition polymerization or this could be non linear in which there might be instead of combining linearly they might be combining in many multiple places essentially creating a network of polymerization.

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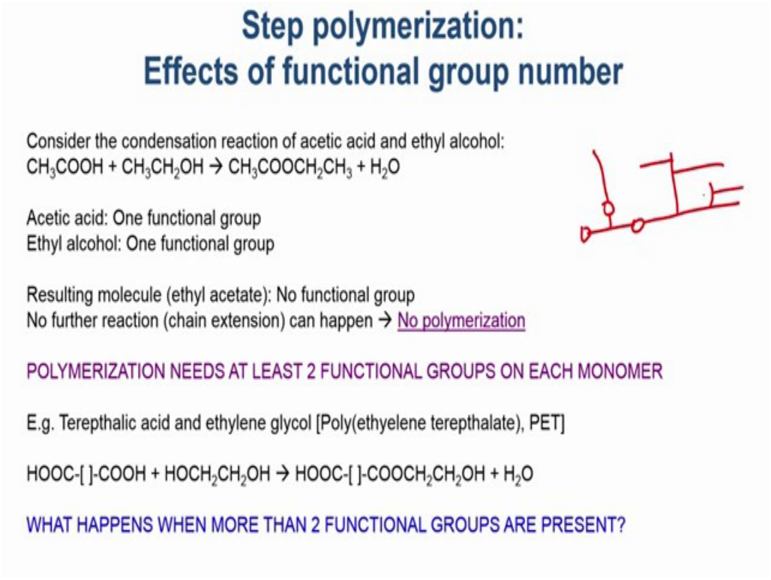

Step polymerization: Effects of functional group number

Consider the condensation reaction of acetic acid and ethyl alcohol:
$CH_3COOH + CH_3CH_2OH \rightarrow CH_3COOCH_2CH_3 + H_2O$

Acetic acid: One functional group
Ethyl alcohol: One functional group

Resulting molecule (ethyl acetate): No functional group
No further reaction (chain extension) can happen → No polymerization

POLYMERIZATION NEEDS AT LEAST 2 FUNCTIONAL GROUPS ON EACH MONOMER

E.g. Terepthalic acid and ethylene glycol [Poly(ethyelene terepthalate), PET]

$HOOC\text{-}[\;]\text{-}COOH + HOCH_2CH_2OH \rightarrow HOOC\text{-}[\;]\text{-}COOCH_2CH_2OH + H_2O$

WHAT HAPPENS WHEN MORE THAN 2 FUNCTIONAL GROUPS ARE PRESENT?

So, what is the effect of functional group? Number on this, so let us consider this chemical reaction. So, we have an acid reacting with an alcohol to give an ester group and also releasing water so; obviously, since there is a release of water this is a condensation reaction. The important to note is that acetic acid and ethyl alcohol which are being used here as monomers they both have one functional group each.

So, let us say that this reaction has happened there is a really no functional group left in the product that is formed, given that there is no functional group in this product the resulting molecule cannot go further reaction. So, no polymerization will further happen. So, essentially all you have done is a simple reaction making a small molecule which is essentially not a polymer.

So, what does this tell us? This tells us that for the polymerizations to happen we need at least 2 functional groups one each of the monomer. So, an example here is the terephthalic acid with ethylene alcohol, so in this case you have groups which contain both the acid has two different acids two different COOH group and then the ethyl alcohol again has two different OH group.

So, in this way whatever the product is formed even though you have used 2 of the functional groups one each on the monomers there are still 2 more functional groups available on the resulting product for it to further continue to react. So, quick thing here is what will happen if you have more than two functional groups in your monomer any guesses then you may have. So, I will give you a moment to think about that.

So, as most of you might have guessed it already, if you have more than 2 functional groups it can essentially reach to branch. So, you can have a situation in which you have a group here; a group here if there is only two then essentially it can only grow linearly, but; however, if there is another group on the monomer which is here it cannot only grow linearly it will also grow in branches leading to a complex network essentially leading a lot of branches in the polymer.

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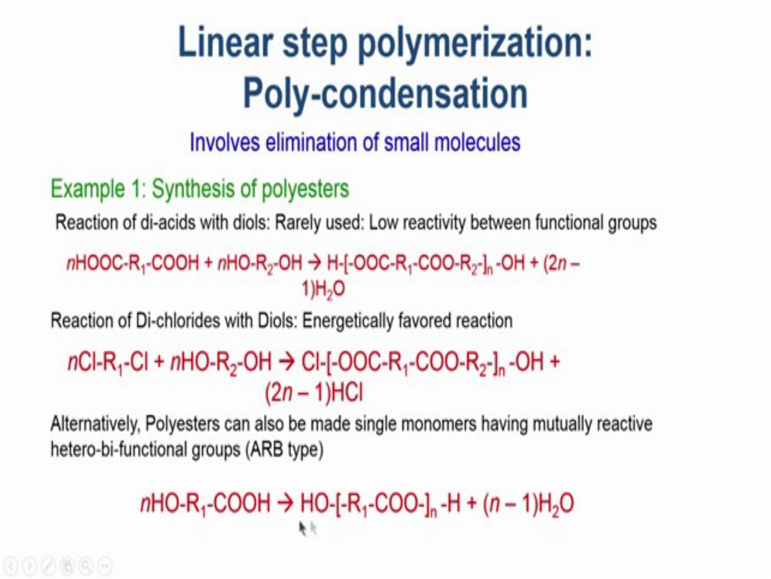

Linear step polymerization: Poly-condensation

Involves elimination of small molecules

Example 1: Synthesis of polyesters

Reaction of di-acids with diols: Rarely used: Low reactivity between functional groups

$$n\text{HOOC-R}_1\text{-COOH} + n\text{HO-R}_2\text{-OH} \rightarrow \text{H-[-OOC-R}_1\text{-COO-R}_2\text{-]}_n\text{-OH} + (2n-1)\text{H}_2\text{O}$$

Reaction of Di-chlorides with Diols: Energetically favored reaction

$$n\text{Cl-R}_1\text{-Cl} + n\text{HO-R}_2\text{-OH} \rightarrow \text{Cl-[-OOC-R}_1\text{-COO-R}_2\text{-]}_n\text{-OH} + (2n-1)\text{HCl}$$

Alternatively, Polyesters can also be made single monomers having mutually reactive hetero-bi-functional groups (ARB type)

$$n\text{HO-R}_1\text{-COOH} \rightarrow \text{HO-[-R}_1\text{-COO-]}_n\text{-H} + (n-1)\text{H}_2\text{O}$$

So, some more examples of linear step polymerization, so now we have been only talking about linear ,this also is examples of poly condensation. So, it means that it will result in an elimination of small molecules. So, here is one example which we have already used in the in the previous slide which is di acids reacting with di alcohols they are typically rarely used they do not have very good reactivity; however, they are used and essentially you will have released a water molecule as well as forming of the polymer.

Another reaction is dichloride with di alcohols this is more energetically favorable because the chloride is a good reactive group and so you will essentially get a very efficient reaction in this in such cases, but in this case as it is a poly condensation reaction you will have a small HCL molecule being released.

And then alternatively, polyesters can also be made from single monomers. So, it does not have to be two different monomers you can have a single monomer containing both the hydroxyl as well as the carboxyl group and then they can react within the same monomers to form a polymer.

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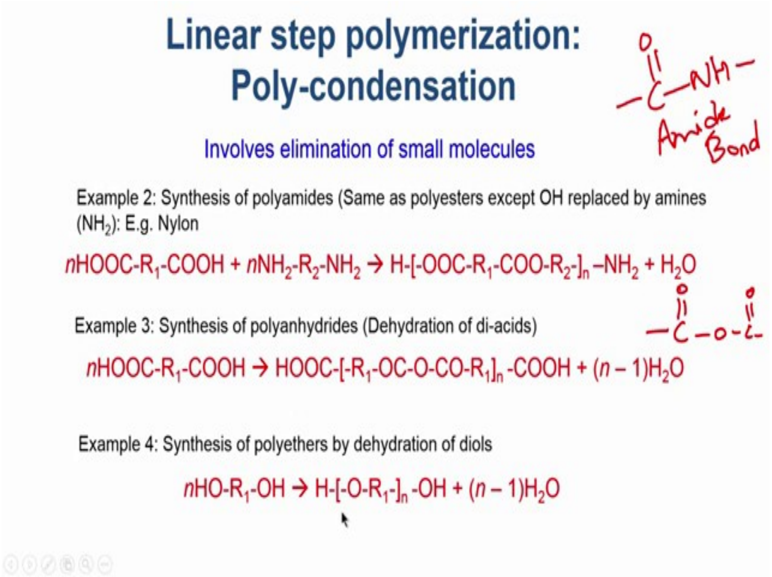

Linear step polymerization: Poly-condensation

Involves elimination of small molecules

$-\overset{O}{\overset{\|}{C}}-NH-$

Amide Bond

Example 2: Synthesis of polyamides (Same as polyesters except OH replaced by amines (NH_2): E.g. Nylon

$n HOOC\text{-}R_1\text{-}COOH + n NH_2\text{-}R_2\text{-}NH_2 \rightarrow H\text{-}[\text{-}OOC\text{-}R_1\text{-}COO\text{-}R_2\text{-}]_n\text{-}NH_2 + H_2O$

Example 3: Synthesis of polyanhydrides (Dehydration of di-acids)

$-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-$

$n HOOC\text{-}R_1\text{-}COOH \rightarrow HOOC\text{-}[\text{-}R_1\text{-}OC\text{-}O\text{-}CO\text{-}R_1]_n\text{-}COOH + (n-1)H_2O$

Example 4: Synthesis of polyethers by dehydration of diols

$n HO\text{-}R_1\text{-}OH \rightarrow H\text{-}[\text{-}O\text{-}R_1\text{-}]_n\text{-}OH + (n-1)H_2O$

Again some more examples here, so this time we are talking about synthesis of polyamides and do you know where the polyamides are seen in our body? Yes if you if you are familiar with proteins all proteins are essentially nothing, but polyamides and what it is a reaction of carboxyl groups with an amine group. So, it could be something we had two carboxyls and one monomer are present and two amines on another monomer represent and they will react to form this amide bond which is a CONH bond. So, essentially this is an amide bond and this will be this will be the reaction that will happen.

Another example here is synthesis of polyanhydrides, so this is reaction of two different acids with each other. So, this could be that you have a monomer R 1 containing to different acids and this will essentially react with itself to form this anhydride group which is again represented as this group and this essentially is an anhydride group and you can have a polymerization happening like this as well.

And then again there are lots of variation another example here is synthesis of polyethers and that is essentially reaction of alcohol with themselves. So, you can have two alcohol that continually react to form a polymer as well.

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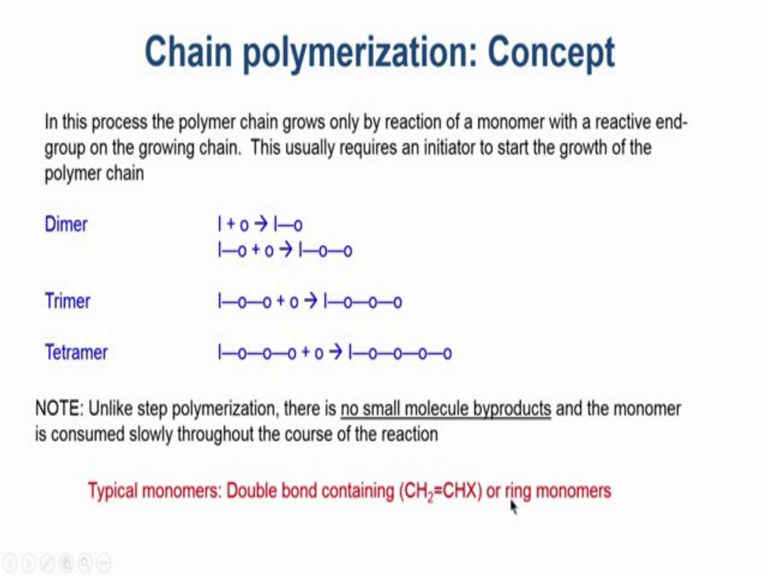

Chain polymerization: Concept

In this process the polymer chain grows only by reaction of a monomer with a reactive end-group on the growing chain. This usually requires an initiator to start the growth of the polymer chain

Dimer	I + o → I—o I—o + o → I—o—o
Trimer	I—o—o + o → I—o—o—o
Tetramer	I—o—o—o + o → I—o—o—o—o

NOTE: Unlike step polymerization, there is no small molecule byproducts and the monomer is consumed slowly throughout the course of the reaction

Typical monomers: Double bond containing (CH_2=CHX) or ring monomers

So some concepts here, let us talk about the chain polymerization now. So, in this the polymer chain grows by reaction of a monomer with a reactive end group, so there is some order to it rather than being random as it was the case in the previous example in the step polymerization. In chain polymerization there is some order to it and I will explain how this order works. So you may have a initiator molecule which is highly reactive , that initiates the growth of these polymer chains.

So, an initiator molecule represented by I here will react with the monomer to form an IO, this IO will then propagate further to continue to react and the way the chain will grow is only in this uniform direction rather than any random combination of different reactants at that at the particular time. Typically, such reactions unlike step polymerization there is no release of by product and so the monomer is consumed slowly throughout the course of this reaction.

So, typical monomers those that contain double bond are very commonly used for chain polymerization also polymers that monomers that have rings in them can be used for chain polymerization with the ring opens up and results in polymerization to occur and we will discuss some examples as we go along.

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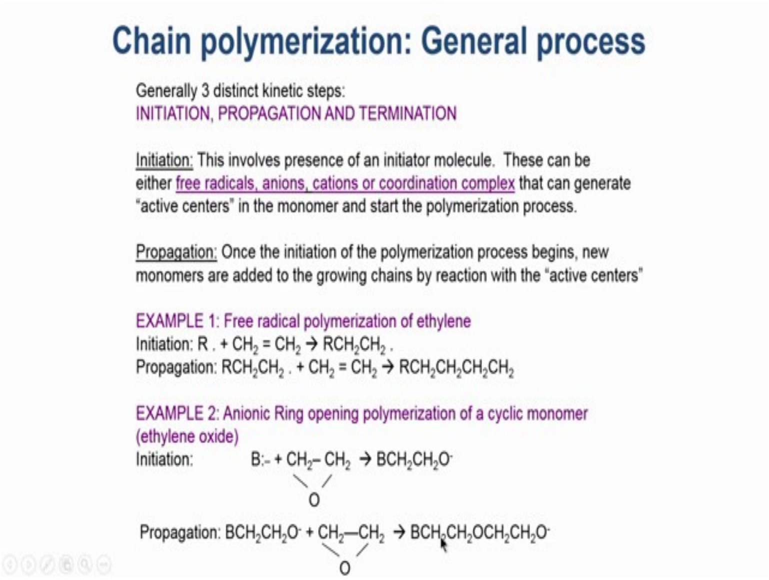

Chain polymerization: General process

Generally 3 distinct kinetic steps:
INITIATION, PROPAGATION AND TERMINATION

Initiation: This involves presence of an initiator molecule. These can be either free radicals, anions, cations or coordination complex that can generate "active centers" in the monomer and start the polymerization process.

Propagation: Once the initiation of the polymerization process begins, new monomers are added to the growing chains by reaction with the "active centers"

EXAMPLE 1: Free radical polymerization of ethylene
Initiation: $R . + CH_2 = CH_2 \rightarrow RCH_2CH_2 .$
Propagation: $RCH_2CH_2 . + CH_2 = CH_2 \rightarrow RCH_2CH_2CH_2CH_2$

EXAMPLE 2: Anionic Ring opening polymerization of a cyclic monomer (ethylene oxide)
Initiation: $B{:}- + \underset{\diagdown\ O\ \diagup}{CH_2-CH_2} \rightarrow BCH_2CH_2O^-$

Propagation: $BCH_2CH_2O^- + \underset{\diagdown\ O\ \diagup}{CH_2-CH_2} \rightarrow BCH_2CH_2OCH_2CH_2O^-$

So, chain polymerization some general process. So, generally there are three distinct kinetic steps we already talked about initiation where you have that initiator molecule reacting with a monomer, so this is an initiate the this generally results in generation of some free radicals, but anions, cations some other kind of complexes which are essentially the active center these are the reactive sites that are going to go find another monomer and react with it.

So, this is the initial phase and this is; obviously, started, so if you want to start a chain polymerization you will have to add a certain concentration of initiator to it, so that these initiation reactions can occur. The next is followed by a propagation, so once the initiation of the polymerization has already happened, propagation is nothing, but these active centers reacting with the monomers and continuing to grow.

So, to again give you an example the initiator in the initiation in this case is you have an initiator containing a free radical which then reacts with let us say here C double bond C react resulting in a product which is combining that initiator with the with the molecule as well as another reactor site at the end of it.

So, this reactor side then can go within react with another double bond to result in a larger molecule and this will continue to propagate as time goes on. Here is the ring opening polymerization reaction, so you have another initiator B here which is an anion and it will go and react with this ring structure to give rise to a larger anion which will again then find another ring structure and this reaction will continue till the reactants are all consumed. So, just as I discussed this propagation will happen as we go along.

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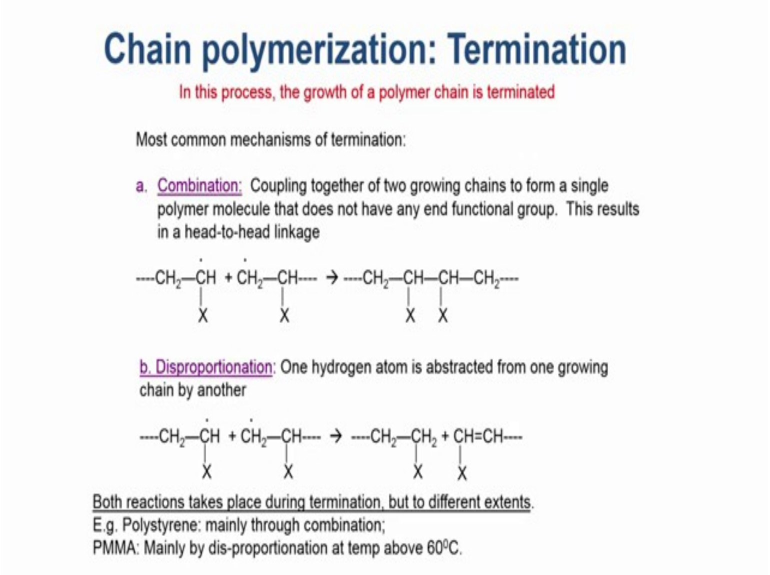

Chain polymerization: Termination

In this process, the growth of a polymer chain is terminated

Most common mechanisms of termination:

a. Combination: Coupling together of two growing chains to form a single polymer molecule that does not have any end functional group. This results in a head-to-head linkage

$$\text{----}CH_2\text{—}\underset{X}{\overset{\cdot}{C}H} + \overset{\cdot}{C}H_2\text{—}\underset{X}{CH}\text{----} \rightarrow \text{----}CH_2\text{—}\underset{X}{CH}\text{—}\underset{X}{CH}\text{—}CH_2\text{----}$$

b. Disproportionation: One hydrogen atom is abstracted from one growing chain by another

$$\text{----}CH_2\text{—}\underset{X}{\overset{\cdot}{C}H} + \overset{\cdot}{C}H_2\text{—}\underset{X}{CH}\text{----} \rightarrow \text{----}CH_2\text{—}\underset{X}{CH_2} + \underset{X}{CH}{=}CH\text{----}$$

Both reactions takes place during termination, but to different extents.
E.g. Polystyrene: mainly through combination;
PMMA: Mainly by dis-proportionation at temp above 60^{0}C.

So, what about terminations and when does it typically stop? So, it can stop when all the reactants are consumed or they can be several the things it can happen, so this is combination. So, it can happen that a one reactive site can instead of reacting to the monomer can react with another reactive site and that will result in the loss of the reactive sites on two different molecules and if enough combinations like this happen all the reactive sites will be consumed.

And another as sometimes this proportion where instead of actually having reacting one of the active site takes up the electron from the another active site and does not really combine with the growing polymer, but still results in depletion of the reactive sites resulting in loss of the polymerization. So, this is called disproportionation.

So, typically both reactions take place depends on what polymers you are using different polymers will result in different kinds of reactions. So, for example, in polystyrene mainly the termination happens through the combination in PMMA another polymer widely used , its typically disproportionation dominates at the temperature above 60 degree Celsius.

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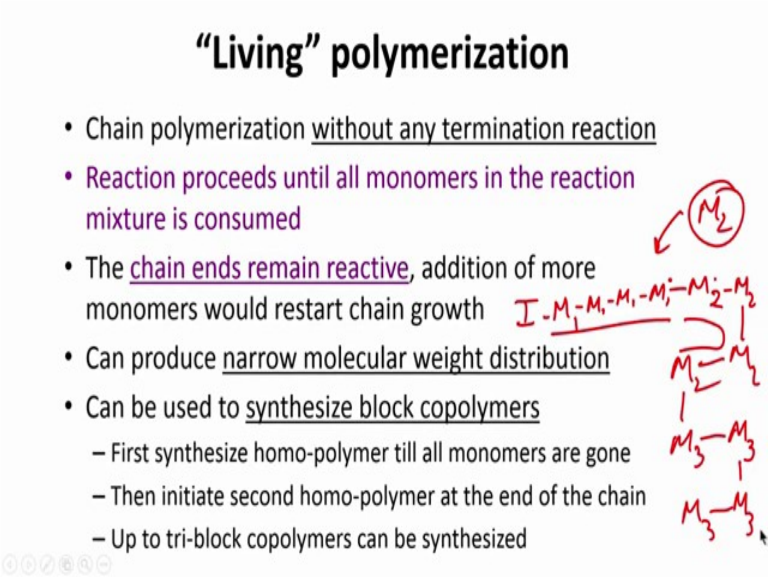

"Living" polymerization

- Chain polymerization without any termination reaction
- Reaction proceeds until all monomers in the reaction mixture is consumed
- The chain ends remain reactive, addition of more monomers would restart chain growth
- Can produce narrow molecular weight distribution
- Can be used to synthesize block copolymers
  - First synthesize homo-polymer till all monomers are gone
  - Then initiate second homo-polymer at the end of the chain
  - Up to tri-block copolymers can be synthesized

And then we have something called a living polymerization, so this is essentially if the chain polymerization continue to go on and you still have reactive sites present, but it runs out of the monomers, then you will still have free radicals the active centers that are available for the polymerization to occur and this is something that we can then use to modify our polymers through different ways.

So, one thing we can do is that the in this case since the chain ends are reactive we can then put in another type of monomer which will then continue the reaction. So, instead of having just a single type of monomer throughout the reaction we can have two different types of monomer arranged in an order.

So, essentially we can synthesize block copolymers because what will happen is you will have a molecule being generated here which is I let us say reacting with monomer 1; monomer 1 continue and then let us say the monomer one finishes at this point, then if you add a monomer 2 to this reaction mixture with the active site already present what will happen is this will then continue to react with monomer 2. And essentially result in a block copolymer because you have a block of M 1 here and a block of M 2 here.

So, that is how you can continue to do this typically you can continue to do this up to try block copolymers. So, you can have another one monomer here M 3 continuing to grow as the reaction is continuing, typically by the time you have finished with three of these different types of monomers there is enough combination and disproportionation termination that has happened that not many active sites are remaining. So, you do not get more than try block copolymers by this method.

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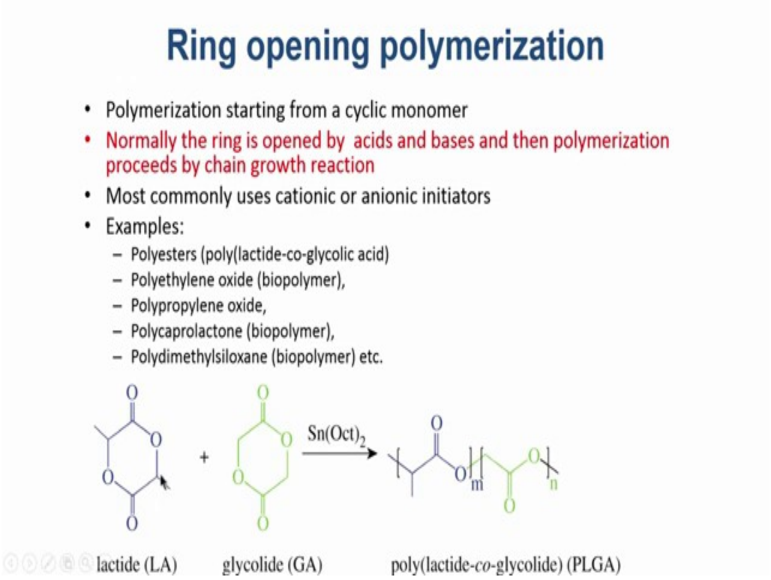

Ring opening polymerization

- Polymerization starting from a cyclic monomer
- Normally the ring is opened by acids and bases and then polymerization proceeds by chain growth reaction
- Most commonly uses cationic or anionic initiators
- Examples:
  - Polyesters (poly(lactide-co-glycolic acid)
  - Polyethylene oxide (biopolymer),
  - Polypropylene oxide,
  - Polycaprolactone (biopolymer),
  - Polydimethylsiloxane (biopolymer) etc.

lactide (LA) glycolide (GA) poly(lactide-*co*-glycolide) (PLGA)

So, just a couple of examples on ring opening polymerization. So, you can have a polymerization that starts from a cyclic monomer and normally the ring is opened by some kind of acid or basis and then the polymerization proceeds by chain growth reaction as we just discussed. Very commonly used with cationic and anionic initiators.

So, some examples are polyesters, polyethylene oxide, polypropylene oxide, polycaprolactone and PDMS all of them pretty much are very widely used for biological applications. And we will talk about most of these as we go along some of these terms you are going to become very familiar with in this course and remember all we are discussing all these polymers because we essentially want to build up some of the basic concepts of what different polymers are there that we can use for drug delivery applications and what are the properties. And once we have some basic knowledge of that , it will help us later in this course to then identify how can we modify them for different applications and requirements.

So, here is a very common reaction I mean this is a PLGA polymer which is very widely used in drug delivery applications and the synthesis of this is through a ring opening polymerization where it you have a lactide and a glycolide group that reacts in presence of an catalyst to give rise to a long polymer of PLGA.

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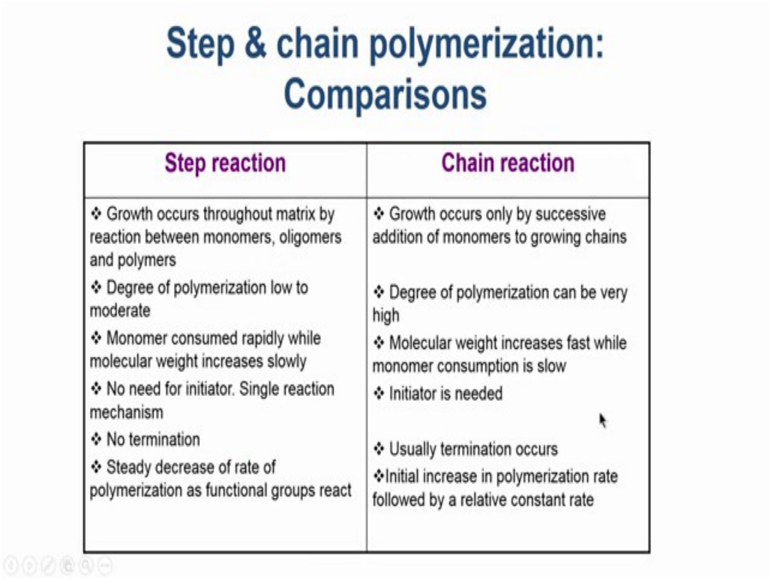

Step & chain polymerization: Comparisons

Step reaction	Chain reaction
❖ Growth occurs throughout matrix by reaction between monomers, oligomers and polymers ❖ Degree of polymerization low to moderate ❖ Monomer consumed rapidly while molecular weight increases slowly ❖ No need for initiator. Single reaction mechanism ❖ No termination ❖ Steady decrease of rate of polymerization as functional groups react	❖ Growth occurs only by successive addition of monomers to growing chains ❖ Degree of polymerization can be very high ❖ Molecular weight increases fast while monomer consumption is slow ❖ Initiator is needed ❖ Usually termination occurs ❖Initial increase in polymerization rate followed by a relative constant rate

So the comparison between the step and the chain polymerization each has its own properties advantage and disadvantages. So, typically for step polymerization the growth occurs throughout in a non uniform manner, so you can have monomers reacting with oligomers forming polymers and all those kinds of things whereas, in chain reaction it is it is much more directional where you will have an active site only reacting with the monomers.

Degree of polymerization typically get with the chain reaction is low and what I mean by that is its difficult to get long polymers through step reaction. But with the chain reaction the degree of polymerization can be very high because you can add very less amount of initiator and the reaction will continue to go on till all the monomer is being consumed has been consumed.

The monomer again is very rapidly consumed just because the reaction is happening at all monomer sites at once, in case of chain reaction in the monomer consumption is much slower, but the molecular weight increases quite quickly as the chain grows.One advantage of the step reaction was is where there is no need for initiator it is a single reaction mechanism, typically most of these initiators we talked about can be toxic because they are fairly reactive.

However, in chain reaction you need an initiator to begin the reaction and so subsequently for drug delivery applications when you talk about using these kinds of polymers you have to worry about, if there is initiator contamination, nonreactive initiator represent there and things like that. No termination step is required, usually the termination occurs through the combination and the disproportionation we talked about, as the functional groups react you have less and less monomer and then the polymerization rate decreases.

However, in this case initially there is increase in the polymerization rate because the initiator is creating more and more reactive sites and then it reaches a relative constant rate till the monomer starts to deplete significantly.

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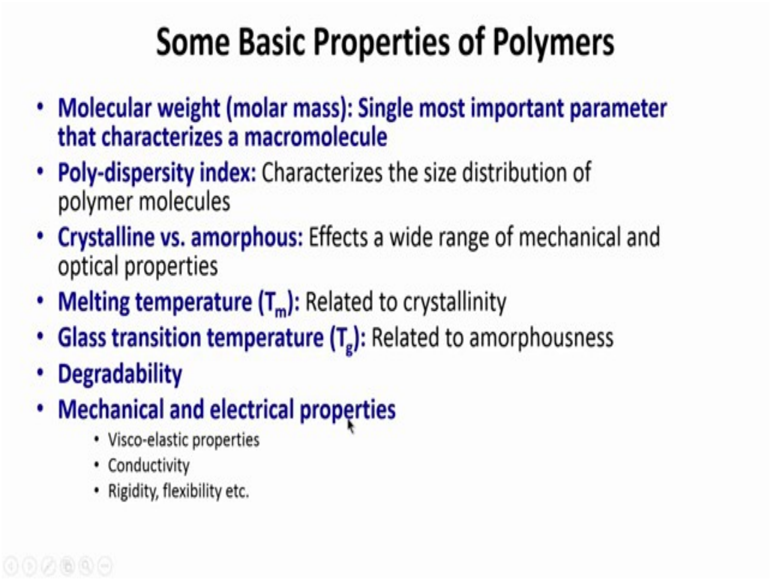

Some Basic Properties of Polymers

- **Molecular weight (molar mass): Single most important parameter that characterizes a macromolecule**
- **Poly-dispersity index:** Characterizes the size distribution of polymer molecules
- **Crystalline vs. amorphous:** Effects a wide range of mechanical and optical properties
- **Melting temperature (T_m):** Related to crystallinity
- **Glass transition temperature (T_g):** Related to amorphousness
- **Degradability**
- **Mechanical and electrical properties**
  - Visco-elastic properties
  - Conductivity
  - Rigidity, flexibility etc.

So, we are going to talk about some basic properties of the polymers. So, the molecular weight is essentially the molar mass is the single most important parameter that characterizes a polymer or a macro molecule.We are going to talk about this throughout this course. Poly dispersity essentially, it tells you what is the size distribution of the polymer molecules.

So, lf I say polymer molecule is 100 kilo Dalton that means, that the average size of these polymer chains is 100 kilo Daltons, but it does not mean that all of them will be 100 kilo Dalton there will be some polymer chains which will be 110 they will be some which will be 90. So, this spread from 100 in this case essentially did it defines what polydispersity index is.

The crystallinity and amorphousness this affects a wide range of mechanical and optical properties or how crystalline or how amorphous the polymer is and again all of this will be discussed in greater details as we go along. The melting temperature which is again related to crystallinity we are going to discuss glass transition temperature if this related to amorphousness we are going to discuss in the next class.

And then of course, the degradability how fast it degrades is very important because that is going to essentially determine how fast the drug is releasing from this polymer or how fast different properties are changing. And of course, for certain applications, mechanical and electrical properties also become important let us say if you are going to use it in bone you want it to be mechanically stable, if you are going to use it for neuron applications you want it to be electrically conductive, so some of those properties also become very important.

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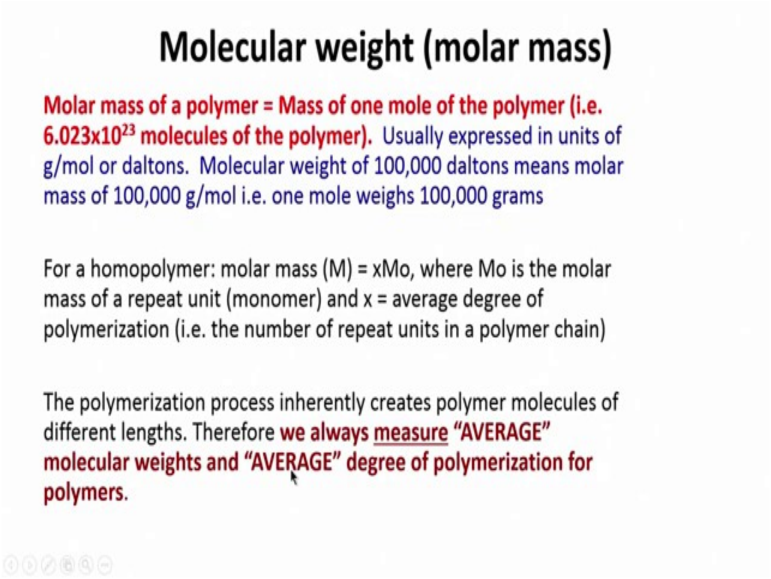

Molecular weight (molar mass)

Molar mass of a polymer = Mass of one mole of the polymer (i.e. 6.023x10^{23} molecules of the polymer). Usually expressed in units of g/mol or daltons. Molecular weight of 100,000 daltons means molar mass of 100,000 g/mol i.e. one mole weighs 100,000 grams

For a homopolymer: molar mass (M) = xMo, where Mo is the molar mass of a repeat unit (monomer) and x = average degree of polymerization (i.e. the number of repeat units in a polymer chain)

The polymerization process inherently creates polymer molecules of different lengths. Therefore **we always measure "AVERAGE" molecular weights and "AVERAGE" degree of polymerization for polymers.**

So, just quickly on the molecular weight, so the molar mass of the polymer is essentially mass of one mole of the polymer as it is for any other molecule. So, essentially; that means, what is the mass of an Avogadro number of molecules of the polymer this is usually expressed in grams per mole or Daltons. So, molecular weight of 100,000 Daltons means the molar mass, essentially one mole has about 100,000 gram of this polymer.

So, for a homo polymer the mass is essentially nothing, but the x times the mass of the monomer where x is the total number of repeat units and then the polymerization process inherently creates polymer molecules from different lengths as I just said you will not get all at the single molecular mass they will all have a distribution. So, typically we always measure the average molecular mass which is essentially nothing, but the average degree of polymerization for these polymers ok.

So, for this course will stop here, we will talk more about the molecular weight in subsequent classes and discuss more about the properties of the polymer in the next couple of classes.

Thank you.