Drug Delivery Principles and Engineering
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Lecture – 07
Biodegradable Polymers and Polymer Drug Conjugates – I

Hello, everyone. Welcome to another lecture of Drug Delivery Principles and Engineering.

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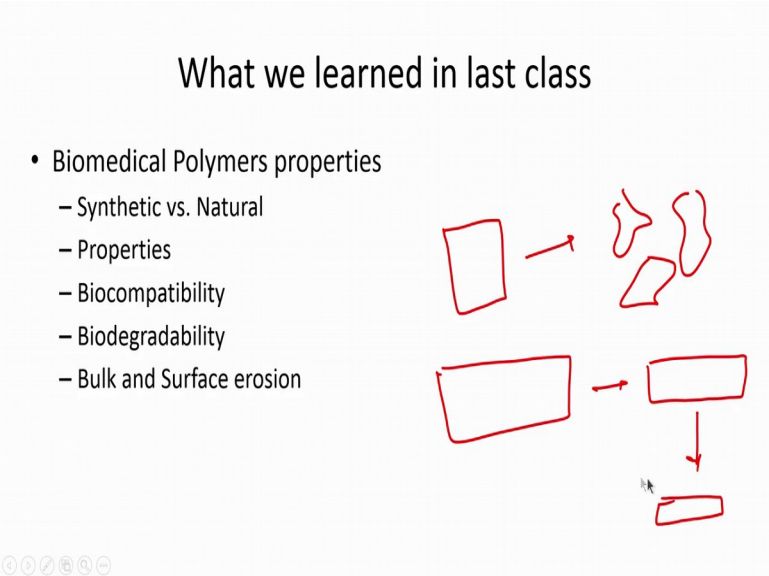

In the last class, we had talked about biomedical polymers and their properties; we talked about synthetic versus natural. So, what are synthetic? Synthetics is something that we are making and natural is something that we derived from some natural form in the nature. Then we talked about various types of properties, what are the desirable properties of biomedical polymers, the mechanical, the chemical, the degradation all those things we discussed here.

Then we talked about biocompatibility. So, whether the polymer is biocompatible or not, whether it elicits immune response, whether the blood over it (Refer Time: 01:09) or whether the blood is stable on it, whether the proteins absorbed to it, all those things come under biocompatibility which will talk further down in the course as well.

Then we also talked about biodegradability, whether the polymer we are choosing needs to degrade or does not need to degrade again depends on applications. Whether the degradation is bulk erosion or the surface erosion, essentially meaning that if it is a bulk erosion then you have the whole device disintegrating in to smaller pieces and again randomly degrading versus if you have surface erosion device and then it will eventually hold it is shape and this kind of degrades from the surface. So, we discussed all of that.

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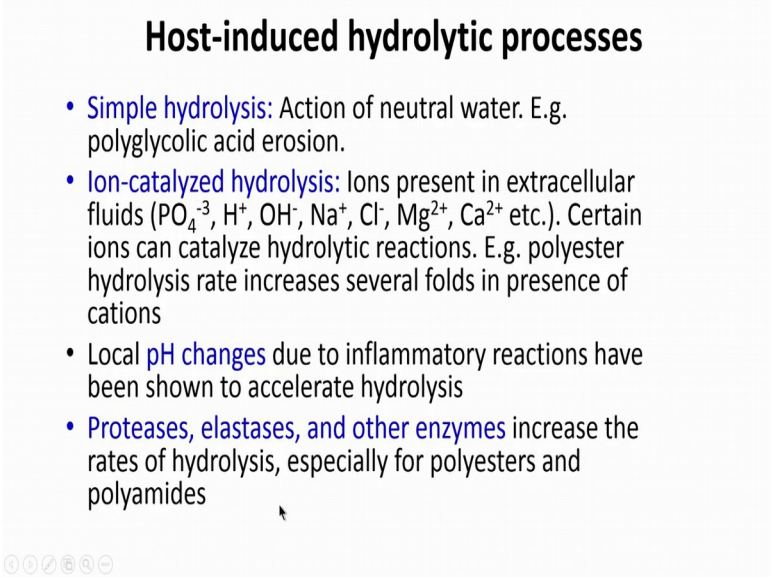

So, now, we are going to move more into the degradation. This was all degradation we talked about in terms of hydrolytic degradation. Here, the host can also cause degradation of these surfaces. So, host induced hydrolytic processes. So, again first of all host contains lots and lots of water. Our body is almost 90 percent water. So, simple hydrolysis always happens in the body. So, polymers like PGA, PLA, PLGA all of these will degrade because the water is present and it is going to act on their chains.

You can have ion-catalyzed degradation. Our body contains lots and lots of ions including phosphate, calcium, magnesium, sodium. So, all of these ions can actually catalyze these hydrolytic reactions. So, typically polyesters which are one of the class of polymers with the ester bond in the backbone. They will have hydrolysis happening through these catalysis mediated by these ions. So, this will essentially increase the rate.

You can have local pH changes. So, of course, what is the pH of the local environment will essentially also affect how fast or how slow these things degrade. So, depending on

what the polymer is, some may have a higher degradation and lower pH, some may have a lower degradation and higher pH. So, all of these will be kind of monitored.

And, then of course, the body contains lots of proteases, elastases and other enzymes. These enzymes are specially designed so that they can degrade whatever their target is and they can also act on your polymers whether natural or synthetic, since most of these degradation backbones contain polyesters and polyamides. So, those things can also cause the host induce hydrolytic processes.

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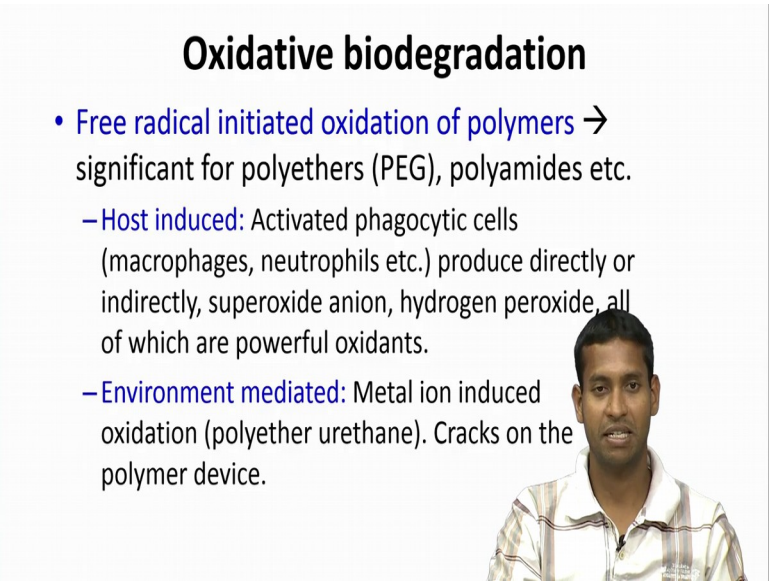

And, then host also has capability to do oxidative degradation. So, that basically means that it generates some free radicals which then oxidized the polymer. Some of the ones that degrade by this processes are polyethers, one of the major class of that is PEG or polyamides which are present again throughout our body as the proteins. All proteins are polyamides.

So, the host induced this could be again as I said it could be host induced. So, you have immune cells which are activated such as macrophages and neutrophils. They will directly secrete these hydrogen peroxides or superoxide anion, which are strong oxidizing agents, very powerful oxidants and in presence of these you will have a faster degradation rate then you will do in vitro if you just put it in a water sample.

And, this could be environment mediated. So, this could be metal ions, they can induce some cracks in your polymer device and things like that. So, all of that is also feasible.

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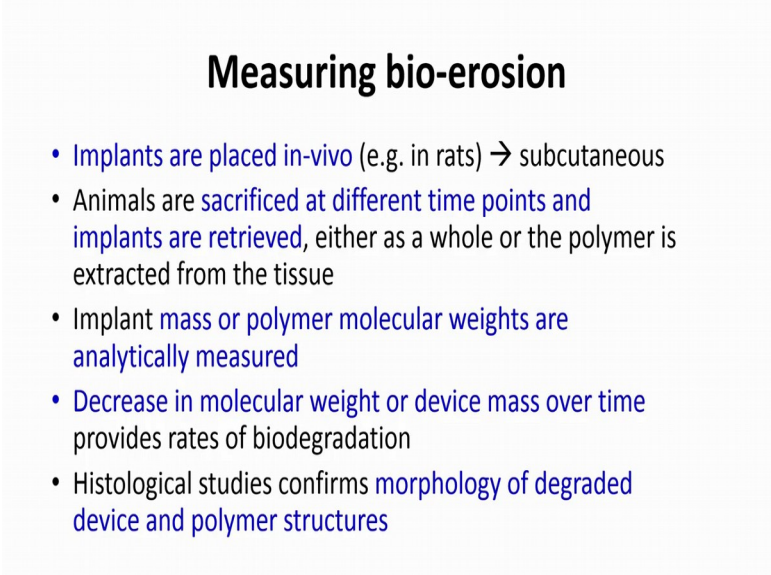

So, how would you measure bio-erosion? So, one way to do it is use some kind of an animal model for example, a mouse or a rat and what you will do is you will place your implant into these organisms at the site that you are trying to test it. So, maybe it might be under the skin or it might be in the blood and then essentially you will sacrifice the animal at different time points, you will take your implant out and see how much of the implant is remaining. So, that is going to give you some ideas to how fast it is degrading over time.

So, then essentially just measure if the polymer change the mass of it you can see how the molecular weight is decreased or how the mass the device is decreased and you can do some histology to see what cells are surrounding that how is the morphology of the device and all of that can be done. So, that is one of the way to measure bio-erosion.

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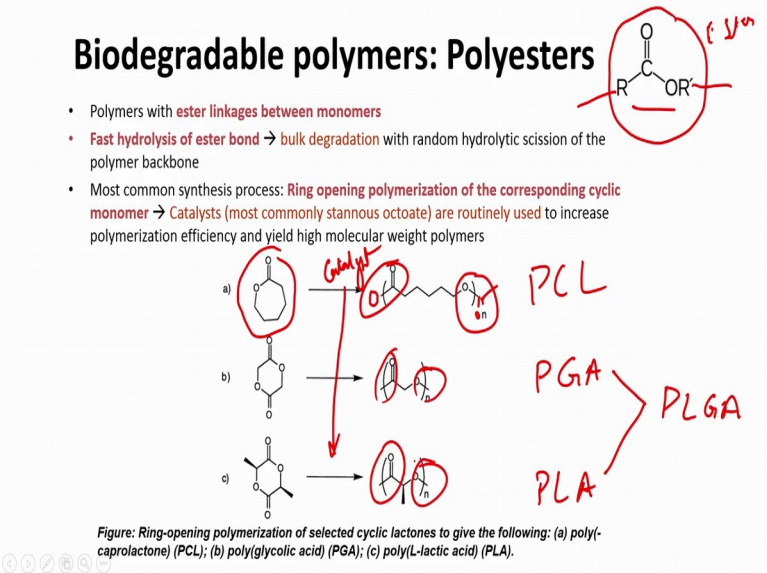

So, in the next few minutes we are going to talk about some of these polymers that are very widely used especially for biomedical applications. This is going to be a list of lots of things. So, I am going to introduce each of these different classes and we will give you some slides which will contain essentially some of the applications for which they are used in the body.

This is essentially for your information. I do not expect you to remember all of this. Some of the common ones you will anyways remember as you go through the course because they will be used again and again. But do not get too worried about seeing a lot of text on the slide. This is just for information so that you have it for any kind of future reference.

So, first thing I will talk about is polyesters. And so, what are polyester, is essentially that contains an ester bond in the backbone. So, these backbones are going to extend in these direction and then this particular group is in ester bond. So, any polymers that contains this in their backbone are polyesters.

So, they are polymers with ester linkages. Essentially as we discussed earlier briefly these ester bonds, they have faster hydrolysis and if they are made from let us say a hydrophilic polymer, then they will experience bulk degradation just because they will degrade very quickly. So, some of the most common synthetic process to make them is using a ring opening polymerization, you put a catalyst and you put some small

monomers with rings in them and that essentially leads to the polymerization via the ring opening. So, this is an example.

So, the first one, all of these we are very widely used. The first one is a polymer called PCL. Essentially you use a monomer which is ring based and you have some kind of a catalyst and that will cause polymerization to happen and if you look closely so, this has a O here and a C double bond O. So, these are nothing, but these are the ester bonds as we just discussed earlier. So, these are polyesters.

Another very widely used polymer is PGA and PLA and then you can combine these two and you can also get PLGA again very widely used polyester one of the most widely used in fact. And, again the same thing happens there is a catalyst present here and then that causes the polymerization to happen and you get ester bonds which will then hydrolytically degrade.

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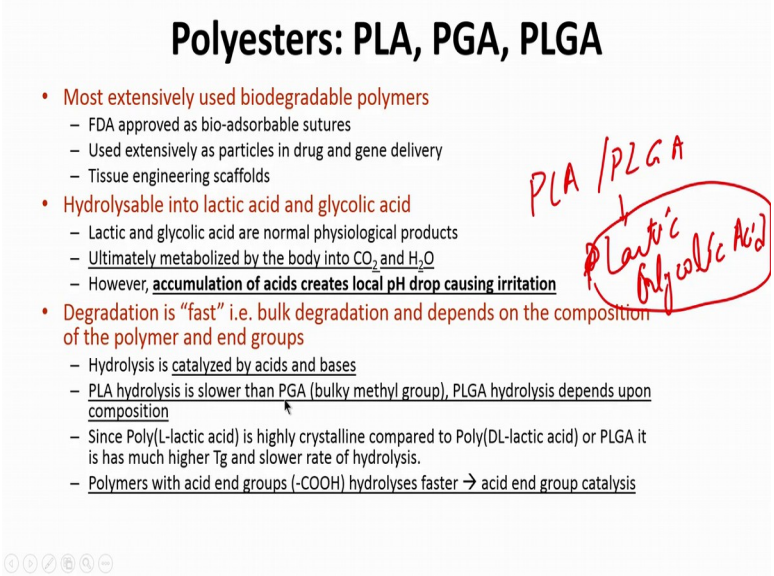

So, as I said, some of the common examples are PLA, PGA and PLGA, it is also FDA approved. So, it is actually being used in humans in lots and lots of devices and we will give some examples as we go along in the course. Very widely used for delivering molecules such as drug or gene although they are also used for tissue engineering scaffolds.

So, what happens is when the ester bond breaks, it breaks into, the PLA or the PGA will essentially break into the individual components such as lactic acid and glycolic acid and which can then be ultimately metabolized by the body to produce CO2 and water. So, that is how their elimination happens from the body.

However, what happens is since we have acid being secreted you can have a situation where locally if it is a big implant then lots and lots of acid is being developed and acid is being developed it causes a drop in the pH that may cause inflammation and irritation to happen. So, you have to basically ensure that not a huge device or not a very fast degrading polymer is being put in because that may cause inflammation and may not be biocompatible at that point.

So, again as I said degradation is fast. It will technically degrade by bulk degradation; however, depending on the sdte chains being used if they are hydrophobic then you can reduce the bulk degradation and shift it more towards surface degradation. This hydrolysis is also catalyzed by acids and bases and ions. So, if you typically the rate you will see for their degradation in water is going to be much slower than what you will see in the body where you have all these ions and all these acids and bases that are present.

So, just an example of how the hydrophobicity will matter. So, PLA a hydrolysis is slower than PGA and the reason for that is PLA contains an extra methyl group, which the PGA does not have. So, that extra methyl groups makes it hydrophobic and that is why the water penetration into a PLA scaffold is slower compared to let us say PGA and so, their hydrolysis will be different. And, then PLGA which is a mixed copolymer of these, its hydrolysis is going to depend in composition, but it is going to be mostly slower than PGA and faster than PLA again depends on the composition that you are using.

Then you can of course, also see which one is crystalline, which one is not those things will also vary the degradation rate. Typically, the polymers with the acid end groups are going to hydrolyse faster, why because now you have acid present in the polymer itself and so, it can self catalyze the hydrolysis through acid end group catalysts.

So, these are all little things that add up and make big changes in the properties and you can use these you can use these small tools and changes to kind of tune your system for whatever application you are looking to accomplish.

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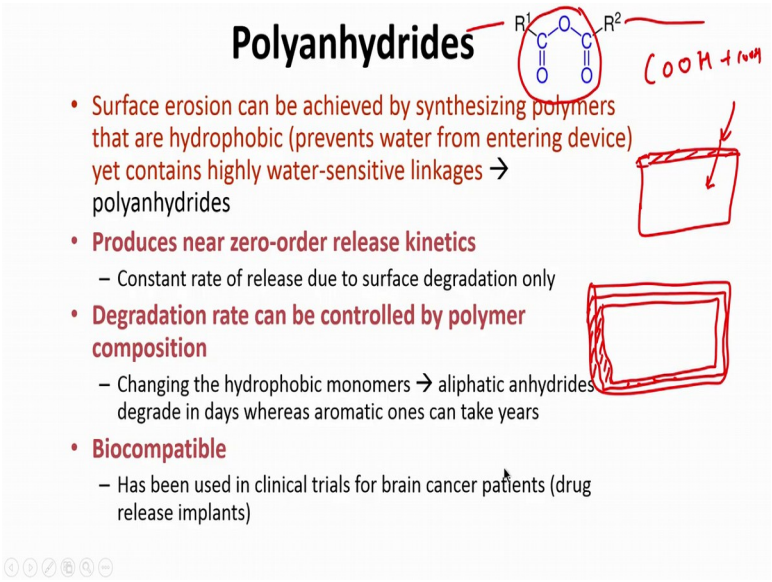

The next class we can talk about is polyanhydrides and essentially, this is an anhydride group and of course, this polymer chains here and here. This is typically formed by a combination of two carboxyls, give rise to this anhydride group. And typically the anhydrides you will find there is surface eroding, they are typically hydrophobic and so, they prevent water to penetrate inside the device and only the water can access the surface of it, plus as I said earlier the anhydrides are very fast degrading functional group. So, even before the water can actually penetrate in the device you will see that the device in contact with the water is gone and so that is why these are typically surface eroding polymers.

Such polymers will typically produce near zero-order release kinetics. So, we talked about this earlier in the course or what is zero-order release kinetics; that means, that whatever is releasing from the implant is constant over time. It is not going to change with the concentration and if you assume that there is a big enough implant, at least for the first few time points you will find that the drug that has come out is very similar over to the next time. But, of course, this is what I am talking about very little time point of over a long period of time the zero-order kinetics will go away, but initially you will find that they are all zero-order kinetics.

The degradation rate again can be controlled by the polymer composition. So, you can change the hydrophobicity, you can add more aliphatic anhydrides that is going to

increase the hydrophobicity. So, you can make them degrade even slower. So, they will degrade over days or if you even make it aromatic which is even further hydrophobic, it may take years. So, these are some of the tools you can play around with.

They are extremely biocompatible. They have been actually used in clinical trials for brain cancer patient to release the drugs. So, in general the compatibility is not an issue in this case either.

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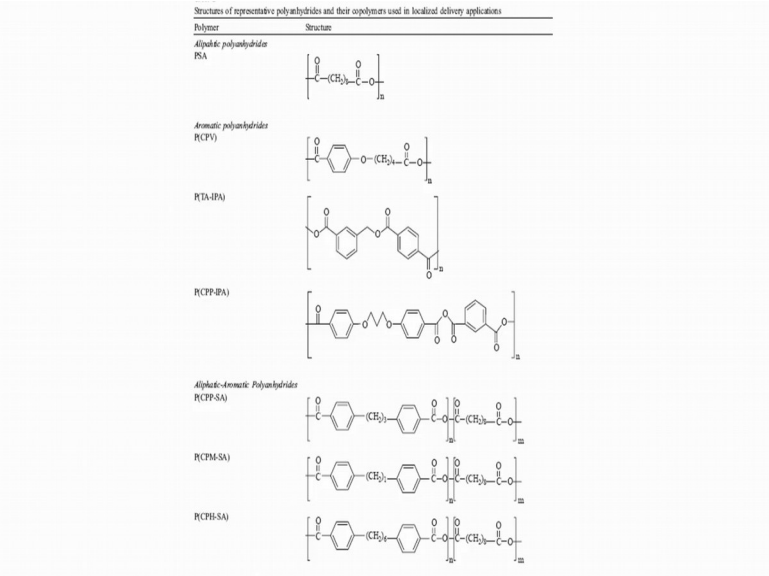

Here is a whole lot of laundry list of different polyanhydrides that are being used for biomedical applications. You can have this slide as a reference. You do not need to remember the names of these.

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Different polyanhydrides studied for various applications as localized drug carriers

Disease	Polymer	Delivery system	Drugs
Cancer	Ricinoleic acid based polyanhydride	Matrix	Methotrexate
	P(RA-SA)	Matrix	Cisplatinum
	P(CPP-SA)	Implant	Bromodeoxyuridine
			N-(phosphonacetyl)-aspartic acid
	P(CPP-SA)	Implant	5-fluorouracil
	P(FAD-SA)	Implant	Taxol
	P(CPP-SA)	Implant	Camptothecin
	P(RA-SA)	Injectable Paste	Paclitaxel
Head and neck cancer	P(FAD-SA)	Matrix	Cisplatin, 5-FU, methotrexate, paclitaxel
Osteomyelitis	P(OA/LAD-SA)	Matrix	Gentamicin
Local anesthesia	P(FAD-SA)	Matrix	Bupivacaine HCl
	P(CPP-SA)	Implant	Dibucaine, bupivacaine
Local infection	P(DDDA-TA), P(BA-PA)	Matrix	Ciprofloxacin hydrochloride
	P(FAD-SA)	Implant	Cefazolin sodium
Restenosis	P(EAD-SA)	Implants	Heparin
Gene delivery	Photocrosslinked polyanhydride	Matrix	DNA
Glaucoma	P(CPP-SA)	Implant	Etoposide
Inflammatory bowel disease	Poly(anhydride-esters)	Microspheres	Aminosalicylates
Inflammation	PLA-PSA-PLA	Microspheres	Triamcinolone
Hormone therapy	P(FAD-SA)	Microsphere	GnRHa
Alzheimer's disease	SA copolymer	Microspheres	Bethanechol

And, then again, here is the different applications they have been used for localized drug delivery carriers. Various types of drugs are being used, various kind of drug delivery systems whether it is particles or whether it is implants, whether it is injectable, all different things are used with all different kinds of polyanhydride polymers for different diseases.

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Synthetic polymers in controlled drug release

Backbone Structure	Examples	Notes
C-C	**Poly(ethylene)** (PE) 	Zero-order temporal control achieved by diffusion from matrices.[125] Tetanus toxoid released by pulsatile kinetics.[126] Prolonged pseudo-first order release of acetoaminopben in gastrointestinal tract.[127]
	Poly(propylene) (PP) 	Biocompatibility improved by albumin grafting to surface.[128] Ophthalmic drug delivery applications.[129] Accurel® used to release agents active in vapor state.[130]
vinyl-based C-C	**Poly(vinyl chloride)** (PVC) 	Membrane devices formulated to release volatile agents into air and non-volatile agents into aqueous solutions.[131]
	Poly(vinyl alcohol) (PVA)	Water-soluble copolymer of vinyl alcohol and vinyl acetate is formed by hydrolyzing poly(vinyl acetate). Surface stabilizer in microsphere formulation.[132,133] Bioadhesive hydrogels.[134]

So, I am just going to give you some more synthetic polymers. I am just going to run through these slides essentially, this is just to give you some idea of how widely these

biopolymers are being used in the current literature as well as in clinics. So, some of them are polyethylene. It is very similar to the plastic that you use to go to supermarkets. Polypropylene, PVC, polyvinyl alcohol all of these and their notes are written on the side. These are different applications again. I do not really want to go into details for any of these slides are here for your reference so that in later on if you need to refer to any of these you can come back to this.

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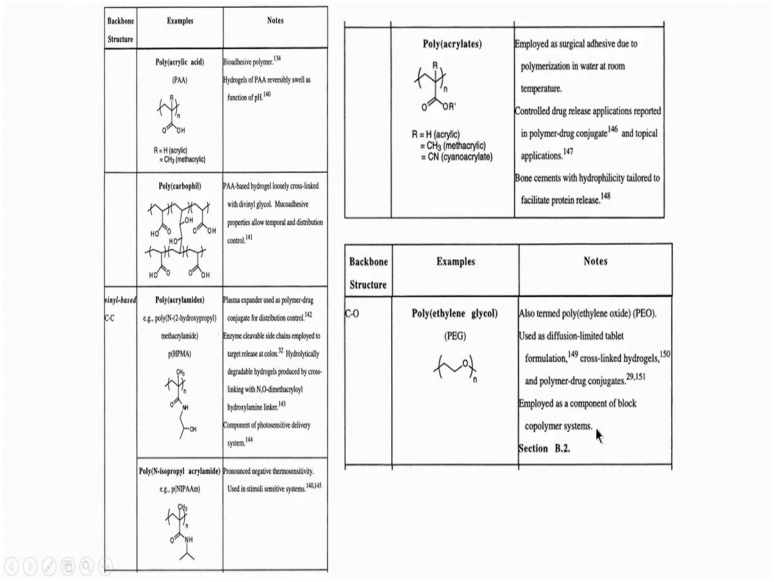

So, some more of these are vinyl based, essentially C-C bond; you can have polyacrylates which are used quite a lot for light based application. You can polymerize them with light, you have polyethylene glycol, very widely used polymer and we are going talk about it in the next couple of classes as well.

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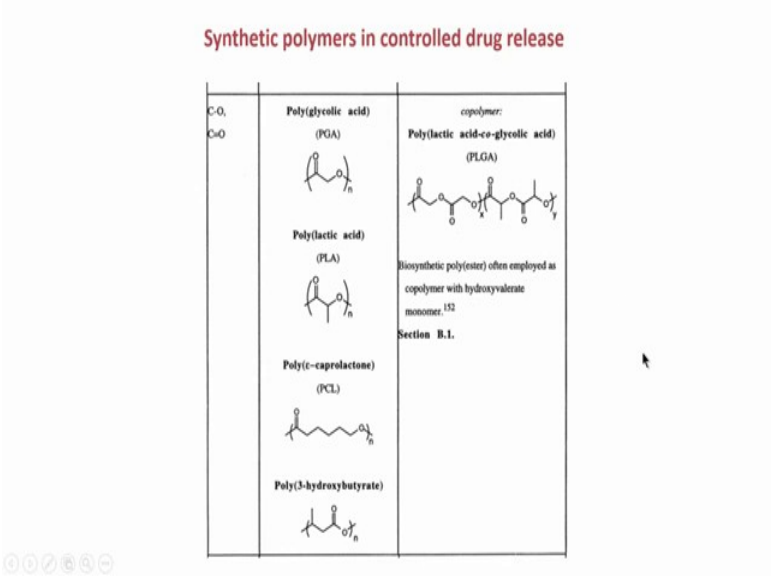

There are some other synthetic polymers for drug delivery, of course, PGA we talked about, PCL we talked about. So, all of these are very widely used. A copolymer PLGA one of the most widely used polymers out there. So, all of these are there.

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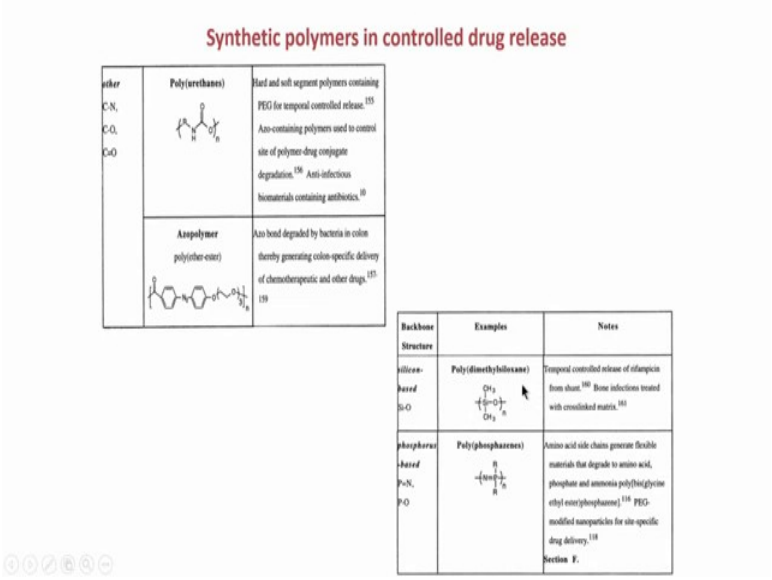

Then you have other applications, polyurethanes used quite a lot for making blood vessels and there are azopolymers. So, different functional groups are different properties in different applications. You have silicon-based implants used for breast implants, phosphorus based implants and quite a bit used in terms of bone applications.

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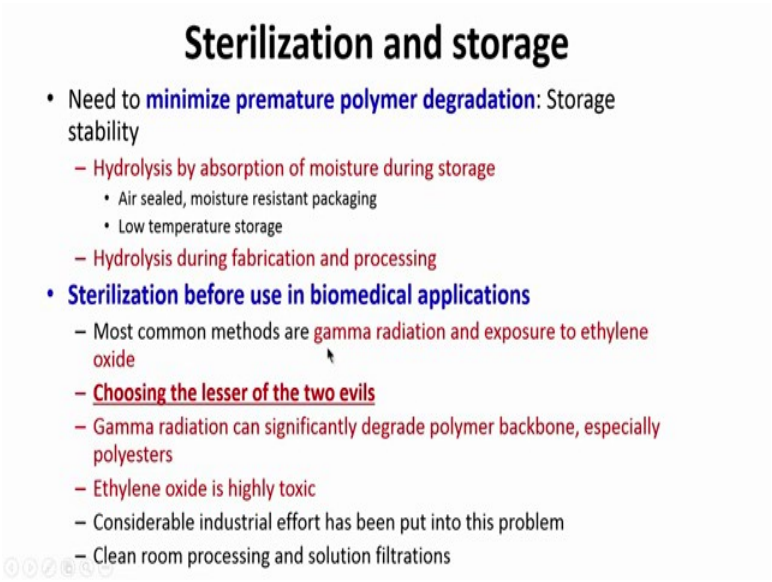

So, all of these are there. Let us quickly talk about their sterilization and storage. So, now of course, if you are going want to implant these materials into a human body or into a live animal you want to make sure that these are sterile because none of your application is going to work if you have some kind of bacteria or fungus or virus present in your system. So, how should you store them over long term; how should you sterilize them over long term, to prevent all these complications from happening.

So, you of course, need to minimize some premature polymer degradation. So, you probably want to store it in dry conditions, you do not want it to have too much of water present which we can then degrade it. So, some air sealed sample, some moisture resistant packaging, low temperature storage, so, if you reduce the temperature the degradation rate is going to go down. That is why you see most of these fancier injections and drugs are actually stored in fridge and freezers.

You have to also consider what is the hydrolysis, it is going to happen in fabrication, and processing of this thing, which is going to take certain amount of time depending on how complex the reaction is. So, all that should be taken into account.

And, then once you have done this, before you use for biomedical polymer there are various sterilization ways. Of course, heat is something that is very commonly used, but a lot of the time these polymers may not be able to sustain the temperature, which are very high above boiling point and things some somethings like that some other common

methods are to use gamma radiation are to expose to ethylene oxide. So, essentially all of these processes are going to affect your polymers. So, it comes down to choosing the lesser of the two evils.

So, of course, you want to kill everything in terms of pathogens there, but you do not want your device to breakdown or maybe it is not able to withstand those kinds of exposures. So, something like gamma radiation can significantly degrade the polymer backbone, especially the polyester, same thing with ethylene oxide. It is oxidizing agent, it is also highly toxic. So, if residual amount is left it can cause toxicity in the body.

So, this is essentially a big problem for the field and lots of effort has went into solving this problem. One of the other solutions are you basically make it such that it is sterile. So, clean rooms have come up. These are rooms which are extremely clean. The air that is coming into the room is filtered. So, if there is no pathogen present in the air then you would not have pathogen in your sample either at the time synthesis or you can filter your solutions and to basically make sure anything of a certain size is cleared out.

So, all of these again as I said are strategies is to ensure that your sample is sterile and are safe for storage.

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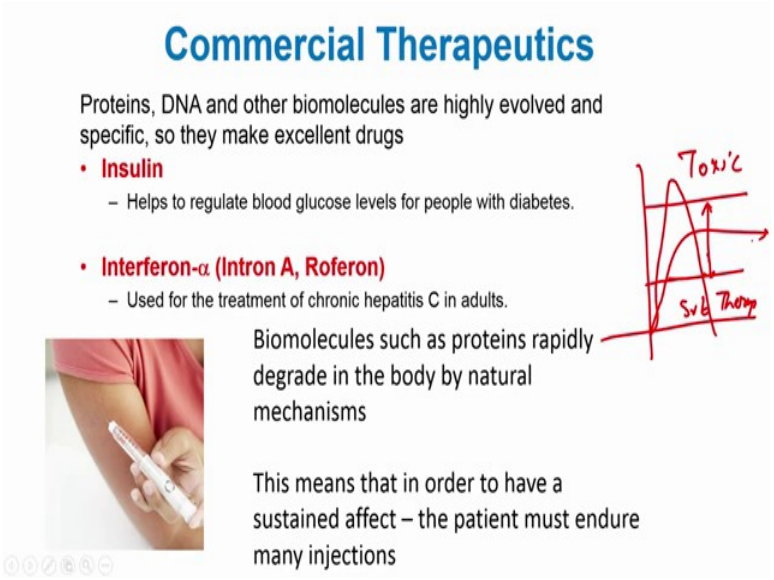

So, we are going to talk about some of the commercial therapeutics and how these polymers will now be used to kind of enhance their effect. So, more and more proteins,

DNA and other biomolecules have been now becoming excellent drugs just because they are very effective and very specific, they are highly evolved.

So, an example here is insulin which is a protein. It helps in regulating the blood glucose level. So, let us say if a person has diabetes you would like to deliver insulin, but the problem is the diabetes is a chronic disease and it is very painful for a person to continuously eat tablet or continuously get injections, not really feasible.

Similarly, other examples is interferon alpha this is used for treatment of chronic hepatitis in adults. So, it is again a small protein that is given, which is interferon alpha that alleviates some of the symptoms that you see hepatitis C.

So, however, another problem here is these biomolecules first of all they rapidly degrade in the body. So, of course, if I take an insulin injection today, by tomorrow I would not have any of that insulin that I had taken through the injection in my system. So, next time I eat, I will have to take it again because these can be get degrade as well as get excreted. So, I have to take several of these to get a sustained effect.

And, we already talked about that dynamics that essentially for every drug there is a therapeutic level and a toxic level. And we always want to be within this range and for as long as possible. So, right now if I take this tablet and injection, I am getting a kinetics like this. However, I would like the kinetics to be more like this.

So, how are these polymers are going to be used for this?

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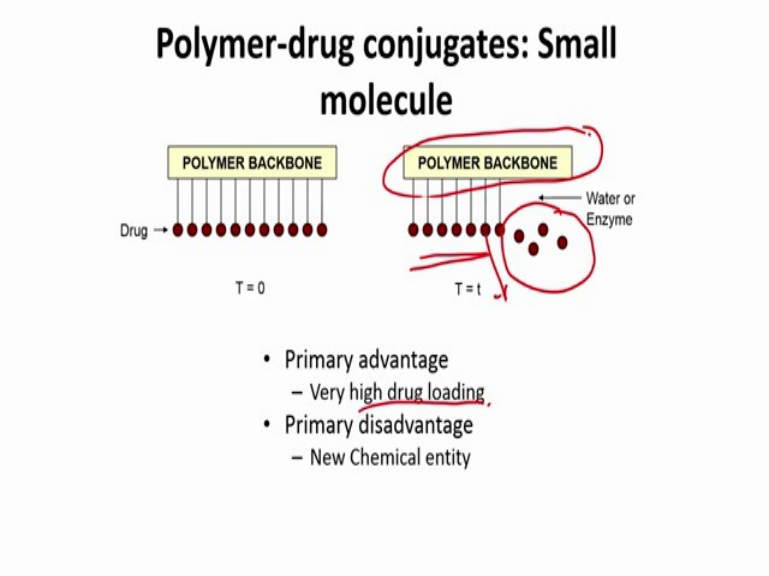

So, one example is polymer drug conjugates. So, very widely used. So, what it is you have a polymer backbone. You take your drug and attach it on to the polymer backbone and once you then inject it in the body what will happen is the water will come in or the enzyme will come in and slowly and slowly degrade these chemical bonds, that formed in backbone and release the drug.

And, the drug will continue to release out in the system till you have this drug attached here and so, what will happen is even though you have injected the same amount that you were injecting earlier just as a free drug, the drug that is available for the system is lower. So, this drug is not going to reach the toxic levels and then because going to take time for it to come out, what will happen is this is going to instead of only remaining the system for 1 hour is going to remain in the system for let us say one day or depends on how big the polymer and how much are you injecting.

So, the primary advantage here is you have a very high drug loading. However, one problem here, a disadvantage here, is now you have attached a new polymer to it. So, it is a new entity, it is a new chemical structure now. So, you have to get a separate approval for this. You have to first make sure that this is compatible and it is going to work in the system.

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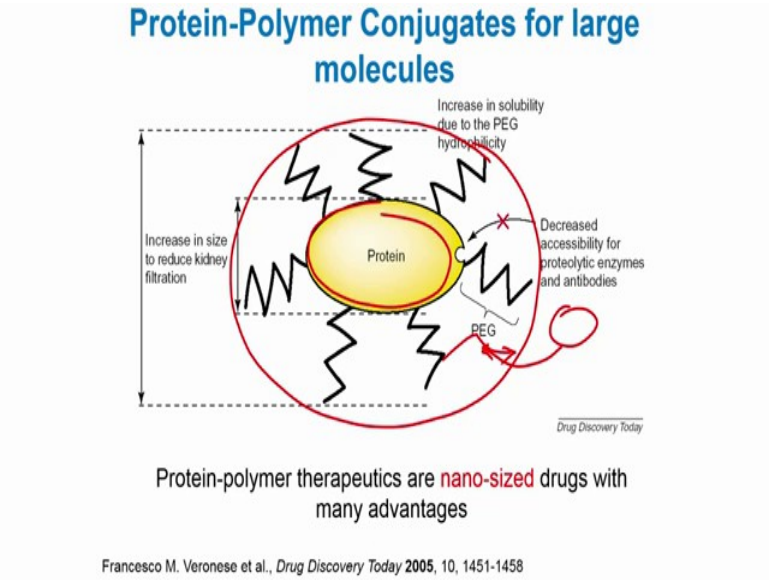

The other way is if let us say the drug is big and the polymers are small. So, let us say you are trying to inject a big protein molecule, but the problem is this protein gets degraded once in the body through action of several proteases, that are present in the body. So, what you can do is you can attach some hydrophilic polymers around it. For example, let us say PEG and then what will happen is, whatever the big enzyme that wants to come and degrade this; it cannot come because this polymer chain repels it.

So, that way you will have a lot more stability of this protein and not only that you have now increased the size of protein. Earlier the protein size was only this much, now you have increased the size to this much. So, maybe now you have increased the circulation time because remember the kidney is going to clear anything which is small very rapidly, as you increase in size the kidney struggles to clear them out from your system.

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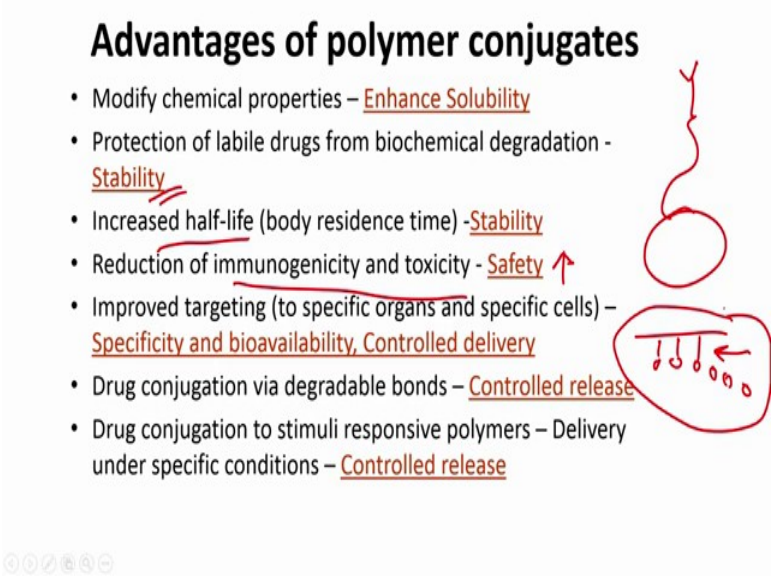

So, what are some of the advantages here? So, one of the advantage is you can also use drugs that are not soluble. So, let us say if your drug was not soluble you cannot inject it in the blood. However, now that you put some hydrophilic polymer on it, the solubility has improved. So, in now you can inject a lot more drug without worrying about the drug precipitating. You can make it more stable just because now the degradation enzyme are not able to act on it. You have increased the half life because now the kidney is not able to clear it because it is larger.

You can also modify you can use very compatible polymers to reduce the immunogenicity and toxicity. So, you have increased the safety and not only that you can actually, on those polymer chains you can put an antibody against your target so that will make it more specific to it. So, it gives you more room to play around on where you want this to go. So, let us say if I only want to target at endothelial cells I can put antibody that binds to endothelial cells and so, that would that would mean that most of my drug ends up closer to the endothelial cells.

And, then of course, you have made it controlled release, instead of all the drug being available immediately, the drug is slowly getting released out as we just discussed earlier. Some of that drug will come out as more and more bonds are going to degrade. So, you have now made a controlled release system. And, you can also make it a stimuli

to responsive depending on what enzymes you are using, if these are only present in the disease site then these will only release at the disease site.

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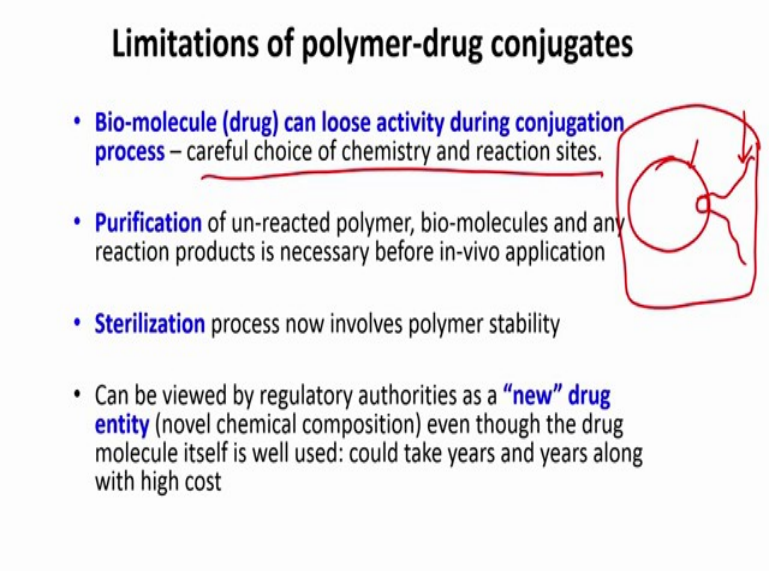

So, what are the limitations of such a polymer drug conjugate system? So, first of all you can lose the activity. Now, let us say if this was a protein you were going to use and here is an active site on it, but now you have conjugated a polymer here and here, this active site can no longer act on whatever it needs to act. So, now you have a risk of losing your activity. So, for that you need to basically be very careful in what chemistry and sites you are reacting it at, that is important.

Now you have to worry about the purification because now you have done a reaction. So, you want do not want the free polymer in the free drug to be present in your system. So, you have got to devise some way to kind of clear those free systems out and so, there is another process that now gets involved. Now, the sterilization becomes a two-body problem right. Earlier you were only worried about sterilization the drug, now you are also worried about how to sterlize the polymer; maybe the drug can sustain a certain temperature and the polymer cannot. So, now, you cannot heat it. So, you have to figure out some other way to sterilize the system.

And, again as I said, typically once you have now chemically conjugated this. This is a new molecule for regulations. So, first of all you have to test its safety, go to the regulatory agency to make sure that it is safe and only then it can be used in the market.

So, it is not like you can just change something and just directly use it in humans, you then have to go through an approval process, which can sometimes take years and has quite a lot of high cost.

So, we will stop here. We will carry further in the next class as to what are the different polymers that can be used for such polymer drug conjugates.

So, thank you.