Drug Delivery Principles and Engineering
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Lecture – 06
Biomedical Polymers

Hello everyone, welcome to another lecture of Drug Delivery Principles and Engineering in the past 5 lectures we have basically gone over some of the basics of the drug delivery, why it is required, what are the different scenarios that are currently used in clinic and what is it that we would like to achieve. Then subsequent classes we talked about one was prodrug and then another thing was we talked about lots of polymers some properties of the polymers.

So, all this we discussed so that we were kind of building up the base before we go into the actual drug delivery concepts that we are going to use for the rest of this course. So, now we are almost ready to essentially talk about some of the polymers that are widely used in drug delivery and how, those are much better or at least give you lot more control for clinical scenarios and we are going to now start going much more deeper into different kinds of mechanisms in different kinds of systems that are out there.

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So, just a quick recap of what we did in the last class. We talked about polymer properties essentially molecular weight how do we calculate that, the number average

molecular weight or it could be the weight average molecular weight, we did couple of exercises and how do calculate different things if we know individual components. We also talked about what is polydispersity and essentially it is a measure of how much dispersion is there between the different molecular chains that are in a system.

We talked about, crystallinity, how crystalline the polymer is and associated, measurement of temperature with that is Tm which is the melting temperature at which point externality is gone. And then for some polymers the crystallinity does not exist, it is only amorphousness and essentially this is again associated temperature with that is Tg.

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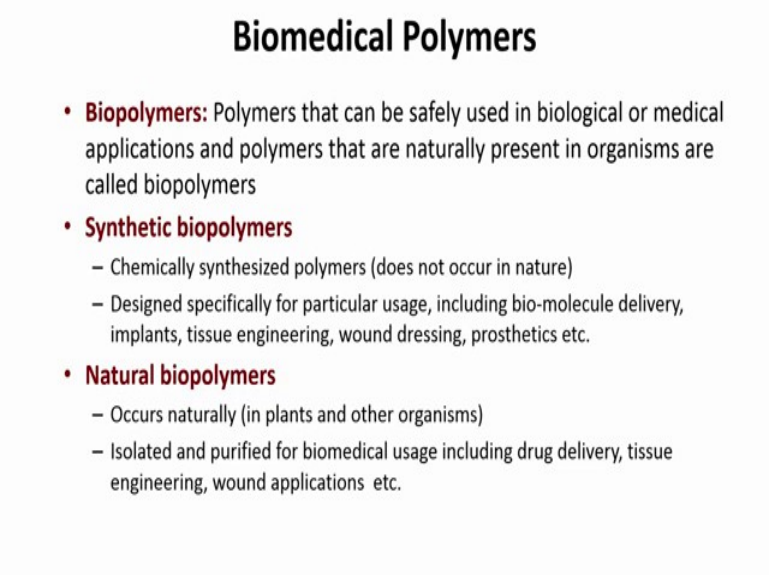

And so now today we are going to talk about biomechanical polymers. So, far again as I said we talked about in general the polymers and it is properties, now we are going to discuss more into biomedical polymers. So, just again quickly defining some of the terms, biopolymers; what is biopolymers. Biopolymers are polymers it can be safely used in biological or medical application. So, typically these polymers are naturally present and hence they called biopolymers.

So, again biopolymers can be divided into 2 different classes, one is synthetic biopolymers and as the name suggests these are synthetic, so did not occur in nature. As it is earlier said biopolymers is something that can be used for medical applications and they may or may not exist in the nature. So, in this case the synthetic bio polymers are

something that we synthesize, these are chemically synthesized polymer, does not occur in nature, they are designed specifically for a particular use of a disease.

So, this could include delivery, this could include tissue engineering, some prosthetics and again we are going to talk about all these as we go along in this course. And then the other class of course, is a natural polymers, which as the name suggests these are naturally occurring. So, these are derived from plants or animals or some other organisms and these are then isolated, purified and then they are used for different applications, just like the synthetic polymers.

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REVIEW

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Advances in Biomaterials for Drug Delivery

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Advances in biomaterials for drug delivery are enabling significant progress in biology and medicine. Multidisciplinary collaborations between physical scientists, engineers, biologists, and clinicians generate innovative strategies and materials to treat a range of diseases. Specifically, recent advances include major breakthroughs in materials for cancer immunotherapy, autoimmune diseases, and genome editing. Here, strategies for the design and implementation of biomaterials for drug delivery are reviewed. A brief history of the

lose their pharmacological activity due to changes in environmental factors such as moisture, temperature, and pH, which can occur in the body or during storage. As the biotechnology industry continues to develop new classes of biopharmaceuticals, improved fundamental understanding of how drug delivery affects safety and efficacy, along with new delivery

So, just before we go into this here is a good review that you guys can essentially go through. It is a very general review about some of the advances that are made in biomaterials for drug delivery. So, just something that I would like you guys if you want more information about this, you can go through this review, although this is not a part of this course.

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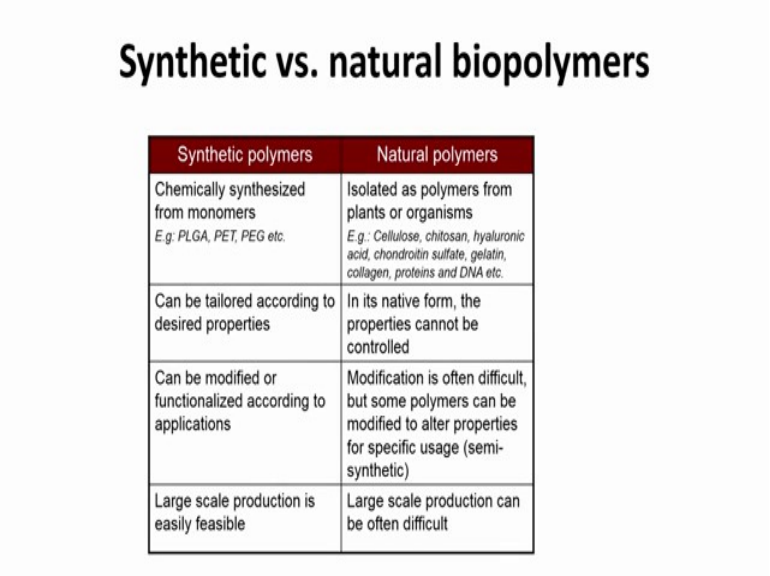

So, again some of the major properties and some of the major differences between synthetic and natural polymers. So, synthetic polymers these are chemically synthesized from their monomers. So, some common examples are PLGA, PET and PEG and many others. Natural polymers are something that I derived from organisms. So, these could be cellulose, chitosan, hyaluronic acid, proteins and DNA collagen one of the most abundant protein.

Synthetic polymers, since we are designing them, we can easily tailor them to different properties. So, let us say if we want a polymer to be faster degrading, we can incorporate that using the monomers which are hydrolytically cleavable at a faster pace, if you want something that has a certain crystallinity we can again choose polymers on the basis of that; however, natural polymers of course, they are the native forms, so, you cannot really change their properties a whole lot. Again, with synthetic polymers since we synthesize them, we can modify them depending on what is the application; however, with the natural polymers although modification is difficult, but then they can still be modified. So, they can be conjugated to different things using some chemistry. So, the modification is feasible although not to an extent which you can do with the synthetic polymers. And then of course, the large scale purification and production is very feasible with these synthetic polymers just because you can make big reactors and the supply is essentially just a monomer. So, as long as you have enough monomers, you can scale it up to whatever amount. However, natural polymers you are kind of dependent on where

to get it from. So, if it is a plant source, you do not really want to cut too many plants. Similarly if it is derived from animals or sea organisms you are essentially dependent on how much is the supply and how much you can extract adult from the nature.

So, typically the large scale production is sort of difficult and they are synthesized in small batches which is another shortcoming that people point out about natural polymers. Because, they are synthesized in small batches, so, each batch is different. Although there are protocols in place, but they are always treated slightly differently and, so, there could be batch to batch variation with natural polymers. Whereas for synthetic polymers you can make a huge batch and you do not have to worry about the batch to batch variability at least for your study.

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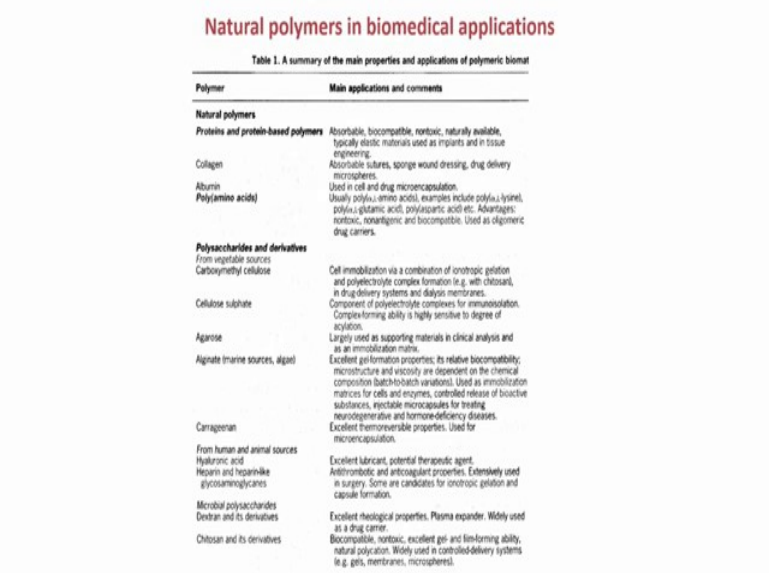

So, some of the natural polymers that are present in biomedical application again the several of them we talked about we give example in the last slide. So, here are some more. So, you have proteins and protein-based polymers, these could be used for different applications such as they could be absorbable, they are of course, biocompatible. Example of the proteins as collagen which is one of the most abundant protein present in the body. This is a structural protein and very widely used in tissue engineering. Another there is albumin this is another protein that circulates through our blood and again very widely used. You can have polysaccharides, these are essentially sugar moieties that are present in our body. These could be agarose which is derived

from a seaweed, this could be alginate, this could be cellulose, several of them and all the different applications are written here. You do not really have to remember all these applications particularly, we will talk about some of these as we go along, this is just for your reference that there are a wide variety of natural polymers that exists and we have used them for biomedical applications quite a lot.

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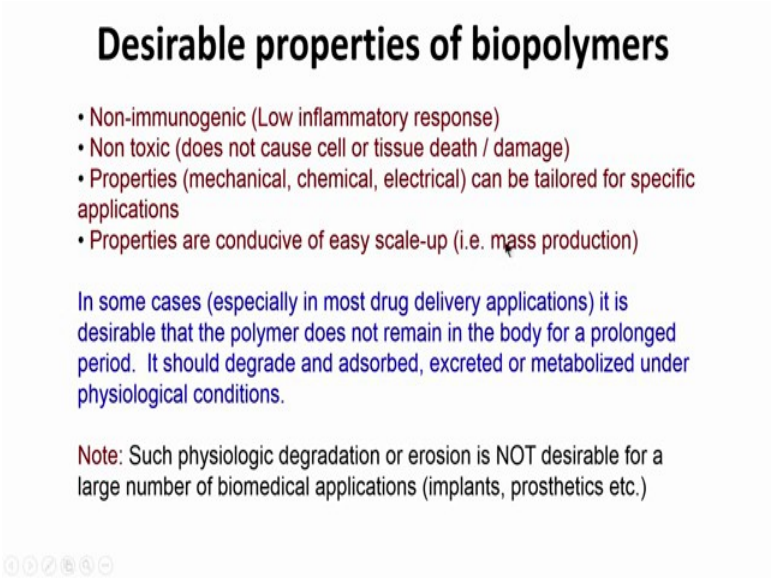

So, what should be the desirable property of the biopolymer? So, one thing is certain it should be non immunogenic. So, of course, if it creates any kind of toxic response in the body and any kind of inflammation in the body then that is a complete no, the patient will never feel better, with those kinds of polymers. So, it should definitely be non immunogenic, it should be non toxic of course, we are trying to cure the patients. So, these polymers should be very compatible that they do not really cause any tissue death or even small damage to the tissue.

The properties again these depend on specific applications. So, what are the mechanical chemical and electrical properties, let us say if I want to put a material that is going to stabilize my bone, I that is a polymer that I need to be structurally very strong. So, I want very high mechanical properties, if I want something to put for our neural implants or something related to brain, they should be able to conduct the signals. So, the electrical properties become important.

So, again all of these properties are important and which one is more critical than depends on the application that we are looking at. And of course, as we already briefly discussed is they should be easy to scale up. I mean it should not be like that we can only get a milligram of that, let us say in a year something of that little quantity is not going to help. So, there should be reasonably scale up I mean we may not be able to get quintals and tons of these materials, but then still depending on the application if we require a certain amount we should be easily able to get that. So, mass production should be easy.

In some cases especially in cases of drug delivery, it is desirable that the polymer does not remain for longer period, I mean essentially let us say if we have a fever and we want a and drug to be given 5 days, this is the maximum we want the polymer to be present. So, in that case these polymer should degrade and come out from the system as well or excreted or metabolized, any of those mechanisms.

So, then the degradability of the polymer also becomes important; however, this is not essential I mean again as I said if you are looking for some structural polymers, something that gives you strength in your bones or something like that you do not want wanted to degrade, at least not anytime soon. So, these are again application dependent.

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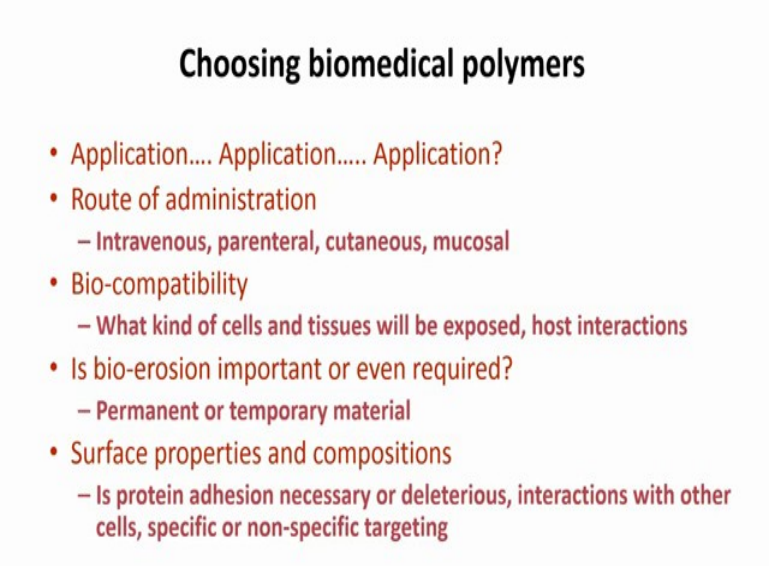

So, as this is a good segway to this slide. So, how would he choose biomedical polymers? So, as we said the major thing is what is the application? So, there are several libraries of these biomedical polymers out there, but the one that you choose will depend

on what is your application. Then there are other things there are what route of administration you are going to use. So, there are several ways you can administer a particular polymer in the body or a particular drug in the body, you can directly put it into the veins, you can take a tablet orally, you can put it under the skin or you can put it some on some mucosal surface like lungs and all via inhalation.

And then there are several others and we will talk about route of initiation in the later part of the course, but again you will choose different polymers depending on what you want to achieve, different sizes of them, different properties all will depend on that. Biocompatibility is a very big term that is being used in the field; however, this depends essentially on where and how it is going to interact with our body. So, biocompatibility for lung tissue might be very different from the skin tissue, which again might be very different from the brain tissue.

So, and this biocompatibility is essentially defined on the basis of the application itself. And then as we discussed, we may also want some kind of degradation to happen so some kind of bioerosion to happen. So, again this again depends whether we want a permanent implant or we want it to be temporarily injected into the body and gets cleared out. And then also what are the surface properties do we want the proteins present in the body to interact with the surface, sometimes we do not want that to happen and again all of these we will discuss. But all of these are some of the properties that we will need to consider before we choose a biomechanical polymer for our application.

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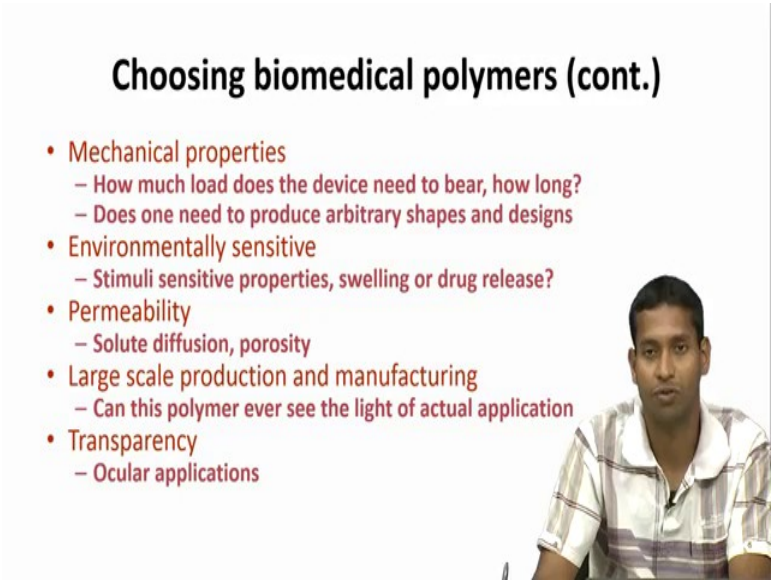

So, further on that again mechanical properties are important. So, how much load does the device needs to bear. So, again as if it is a bone implant you need it to be structurally very stable, if it is something that you are just putting into the skin, for something to release out it does not really need to bear any kind of load on it.

So, the mechanical properties of those implants will be very different, do we need a defined shape or the shape is not very important all of these become important in that case. Whether we want it to be environmentally sensitive and what essentially; that means, is there are polymers which will respond to the environment they are in, let us say, if it is a diseased environment they may behave differently than in a healthy tissue.

So, that allows us to kind of make it very disease responsive. So, only the drug will come out if there is a certain kind of a disease symptom that is present maybe it might be high temperature due to fever, it might be low pH at the site. So, all of that becomes important and again all of these things we are going to go further into details as we go along in this course.

Then we have permeability. So, whether we want these polymers to be permeable, things may come in and out in these polymers, large scale production we again talked about earlier and then whether we want them to be transparent. So, if let us say we are designing something, as a eye lens or a cornea we want them to be transparent in other applications, we may not care. So, again it just essentially depends on what is the

application we want and depending on that there are several properties that we will have to consider before we choose what kind of polymer to go with.

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Again, this is a laundry list of lots of things. I do not expect you guys to remember this. This is just for information and this will be present in the slides. So, you can go through these. These are polymeric properties need for specific biomedical applications. So, there are several of them listed here dental, ocular, orthopedic vascular and several others. So, you can just go through that for your own interest and in free time this is again not something that you guys should remember.

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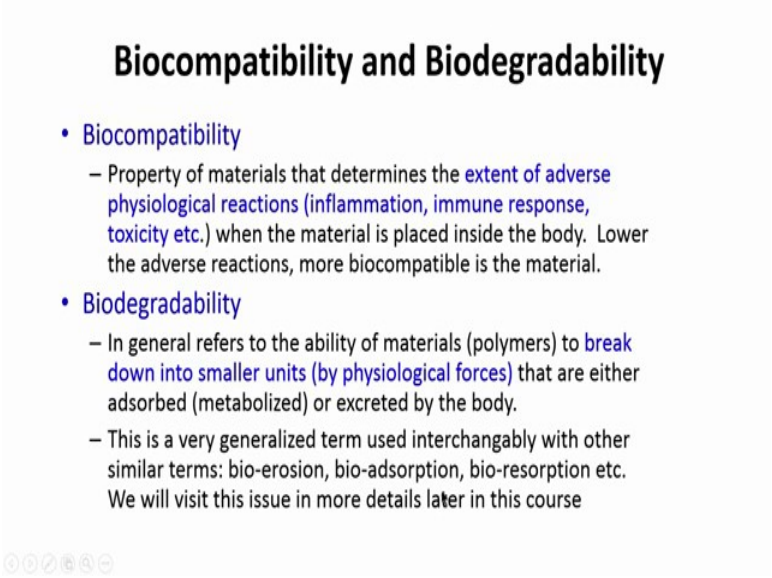

So, let us define some more terms we have biocompatibility and biodegradability. So, what is biocompatibility as we mentioned previously it is a property of the materials, how they are interacting with the body, whether they are causing any kind of adverse reactions such as inflammation or toxicity, when they are placed inside the body.

So, eventually for any application, we would like the biocompatibility to be high and which essentially means that they are causing less and less of these adverse reactions. This is very application dependent. A material may be very compatible in let us say eye, but may not be very compatible let us say in liver. But even then we can use the material in the eye if we want, but then it does not mean that it is completely biocompatible it just means that it is biocompatible for the certain application.

And biodegradability is essentially refers to the breakdown of the polymer into smaller units which can either be then excreted or get absorbed into the system. This is a very general term and then the several related terms that you will hear in the field, some of them are bio erosion, bio absorption, bio resorption and we will talk about this as we go along in this course. But essentially all of them have similar meanings although there are certain differences that exist between these terms as well.

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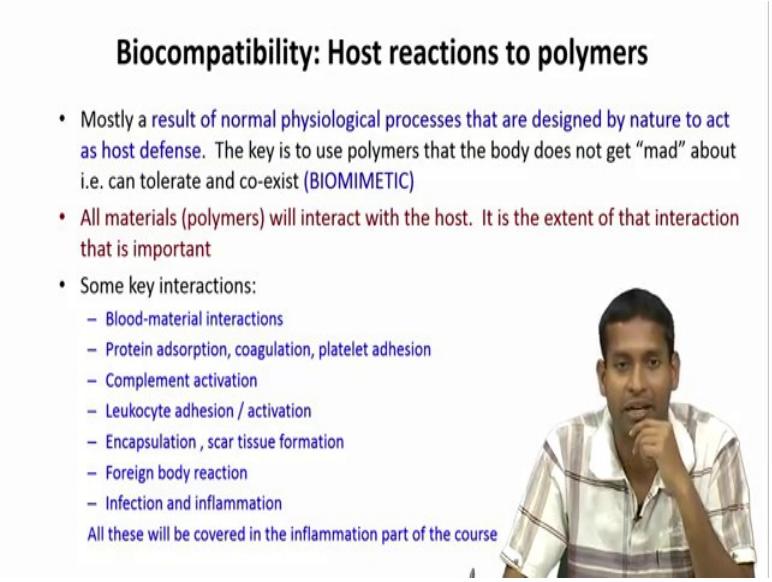

So, biocompatibility, let us talk about hosts reactions to the polymers what are the different things that may go wrong or what are the different things we need to take care about it. So, essentially this is a result of how a physiological process kind of acts on a new polymer or a new material that you put inside the body and the key here is that the material should be compatible enough, so that the body can tolerate it and coexist. So, it could be biomimetic if you want to call it like that or the body should not really consider it to be a threat to itself. All material that you put in the body are going to interact with the body, what is the extent of this interaction is basically what is important. And not only the extent but what whether the extent is positive or negative or neutral is also very important.

So, some of the key interactions when you put things in the body is of course, there will be blood present at that site that you are going to implant it. So, the blood will interact with your material the blood contains several proteins and platelets. So, what how they interact with that surface becomes important, the blood also contains several components of complement system, which is immune response against foreign things. It is one of the immune responses that body generates. So, how those complement proteins tackle the material that you put in is important, the immune cells leukocytes how they are adhering when they get activated. Sometimes what the body does it is it does not like the material and it wants to just completely wall it off and so that is called encapsulation of scar

tissues. What it will do is if it cannot clear it by itself, it will just surround it with lots and lots of proteins and cells and essentially kinds of isolated from the rest of the body.

So, that is called encapsulation or foreign body reaction is also an advanced stage of that and it could also be in terms of infection. So, whether your material may contain something pathogenic that may infect the body. So, all of these topics will be covered in much more detail when we go to the inflammation part of this course.

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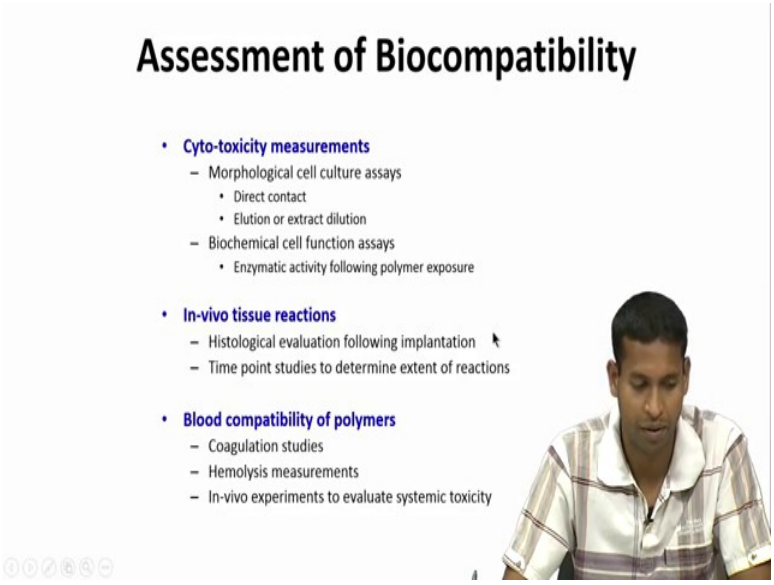

So, assessment of biocompatibility; so, again there are as I said it depends on application and there are several ways to go about with it, the first is before you put it in the body you can test it with some of the cell lines some of the cells that you may have access too.

So, you can put your cells on the material, you can see how whether the cells survive or they die, you can take the degradation product of these materials and expose them to cells to see what response do the cells give once they are exposed to materials from your particular biomedical polymer. You can look at the biochemical function, you can see how the cells are producing different enzymes whether the cells can perform their normal function let us say if it is a bone cell whether it can deposit calcium and mineral. Then you can; obviously, go in vivo you can put it in the body, you can use some small rodent models for that and you can then kind of do histology, which essentially means sectioning out the area where you put it and see how is the body responding to it compared to the healthy tissue itself.

And so, you can do it at different time points to determine, what is the extent of the reaction and how the reaction is proceeding over time. And then of course, you can get access to blood and then test the blood out on these polymers, see whether the blood is clotting on it, whether the blood cells are lysing on it where it is causing any kind of systemic toxicity.

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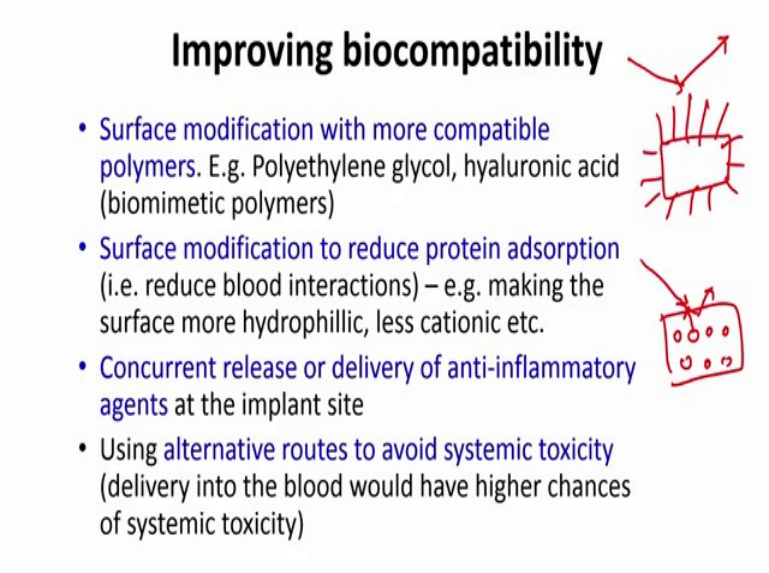

And let us say you want to use a material that is not really biocompatible, what would you do. So, there are strategies out there which will help you make it more compatible then it is. So, you can modify it with some surface. So, you can take a highly biocompatible polymer such as polyethylene glycol or hyaluronic acid and just coat it on the surface. So, what will happen, is the body will only see the new surface, let us say this is your material and I have put PEG chains all around it. So, now, the body can only see the PEG chains when any cell comes and it feels that this is compatible and it just goes away it does not really do anything adverse to your implant. And so, that basically causes you to improve the biocompatibility of the implant that you want to use. You can again surface modify it further. So, let us say you want to reduce protein adsorption. So, again the same strategy will be useful you can code it with some of these materials and we know that the protein adsorption on these ones is low. So, in general your device will now have lower protein absorption. You can then also device strategies where let us say you cannot prevent the cells to come and attach to it. But what you can have, is can have a device that is carrying anti inflammatory molecules in it, which then slowly gets

released out. So, let us say even if your immune system is coming in and interacting with it, which you in the first place did not wanted, but then with these molecules coming out into the immune system, they will tell the immune system to calm down, do not act as if this is a foreign object and that will improve the biocompatibility of your material. Or you can use some alternative routes, let us say if you only want to treat a local disease, lets say it is a wound on the hand, maybe you do not need to inject it in the whole body you can apply it topically. So, you can change the routes of delivery to avoid kind of systemic toxicity and again as I said all of these things depend on applications and here we are going to talk about some general strategies before we go into applications of different things.

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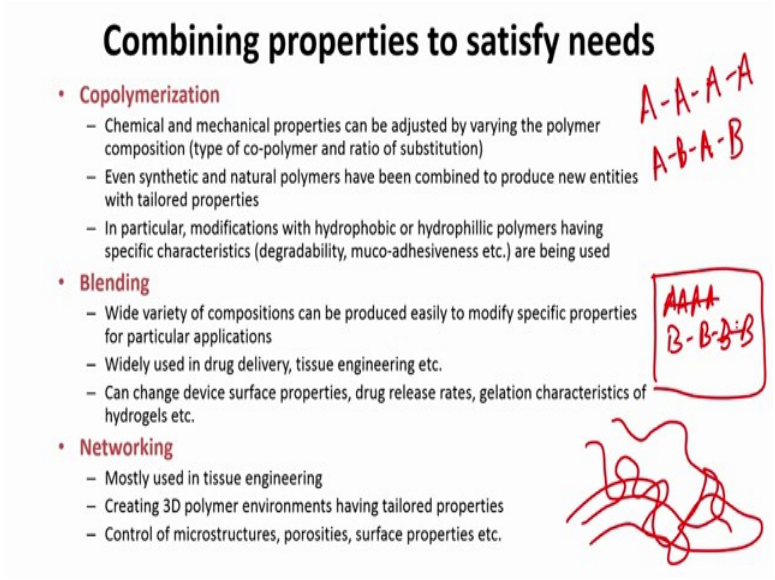

You can also combine properties to satisfy need, you can have co polymerization as we talked about, let us say you initially going to use A-A-A polymer.

So, A is the monomer and you are going to make a poly A, this poly A works very well for you for everything that you need for an application except that maybe it is not very mechanically stable and you want the mechanical properties to be enhanced. So, what you can do, you can co-polymerize it with let us say A-B-A and maybe B is more structurally stable. So, the copolymer is somewhere in the middle, but it improves the mechanical properties enough so that you can use it. So, that is just one example, but you can do the same with chemical properties. All of these can be adopted to kind of improve

the properties for your own application. So, as listed here chemical and mechanical products can be adjusted, you can even combine synthetic and natural polymers there is no reason why you want to keep it completely synthetic or completely natural.

So, if one of the property for natural polymers is better you can use that and combine it with synthetic. In particular, you can modify hydrophobic and hydrophilic groups to attain different kind of degradability, different kind of interactions with the body and all of that is feasible.

You can blend things. So, you do not really have to copolymerize let us say you are going to use a big implant that is made out of A, you can just blend B in it. So, let us say this is one polymer chain, you can just blend the polymer B, into this and that will still improve the mechanical properties or whatever you are trying to achieve, maybe we want a faster degradation. So, this will degrade faster because that lets sasy B degrades faster. So, all of that can be achieved and this is again very widely used for drug delivery and tissue engineering, I am going to talk more about that. And then you can network things. So, mostly used in tissue engineering for creating a 3D polymer environment having tailored properties.

So, instead of having them as separate, you can have chains of A and then you can network this with let us say chains of B going right through them. So, that can also be achieved.

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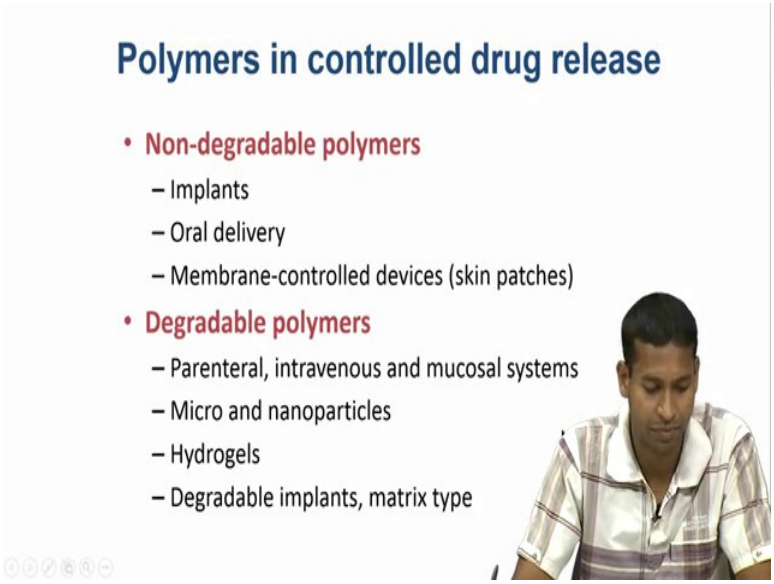

So, let us talk about polymers and controlled drug release. So, what are the different polymers that are used? So, of course, there are non-degradable polymers such as implants and things you use for oral delivery because you know that these things are going to get excreted out and then a membrane control devices such as skin patches. So, you just put it on the skin let the drug come out and then, once the time period is over or disease is cured you can just remove the patch.

So, these you do not really want them to be degradable, they can stay wherever they are and when you are done with them you can just remove them out. Or these can be degradable polymers. So, again this is where the most of the research is currently going on, more fancier systems. So, these are something that you are going to actually inject into the body let us say you put it in the blood, you do not want to circulate in the blood forever you cannot really remove once you injected into the blood because you cannot drain out the whole blood in a human or in an animal or let us say you put it on a mucosal systems.

So, these are something once you inject them, they are there, unless the degrade. So, most of the time you will want them to be degradable polymers. So, unless you are making micro and nano particle, they are too big to remove from the body unless they break down. So, you want them to be degradable, hydrogels is another class of polymers we are going to talk about. Any degradable implants and matrix type of polymers that again, will be discussed later in this course.

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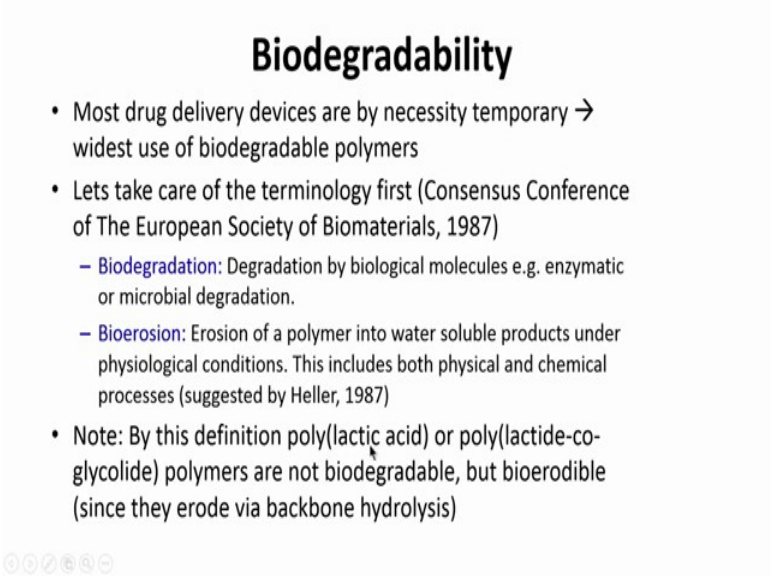

So, biodegradability, again most drug delivery devices are typically temporary because you are trying to cure a disease and once the disease is cured you do not want that device to be there anymore. So, that is where the widest user biodegradable polymers is and let us get the terminology right as we talked about 3, 4 slides back. So, biodegradation is nothing, but degradation by biological molecules, this could be enzymatic this could be microbial. Bioerosion on the other hand is the erosion of the polymer into the water soluble products and the physiological conditions.

So, this could include both physical and chemical processes. So, technically speaking bioerosion is a wider term and biodegradation is a part of it. So, if it is something that is hydrolytically cleavable by water, it comes under bio erosion, it is not into biodegradation, but you will see that this field has grown enough, and there are so many papers and so many literature talking about hydrolytic degradation as also biodegradation.

I just wanted to kind of introduce you to this concept; however, you will see both these terms being used very interchangeably. Another note here is a polymer that you can talk quite a lot about is PLGA or PLA and that is something that is not biodegradable, but bioerodible. But again, if you look into the literature, you will find that people talk about PLA being biodegradable all the time.

And now it has come to the point that it is being accepted that bioregion biodegradation can be used interchangeably; however, strictly speaking, bioerosion is different from biodegradation.

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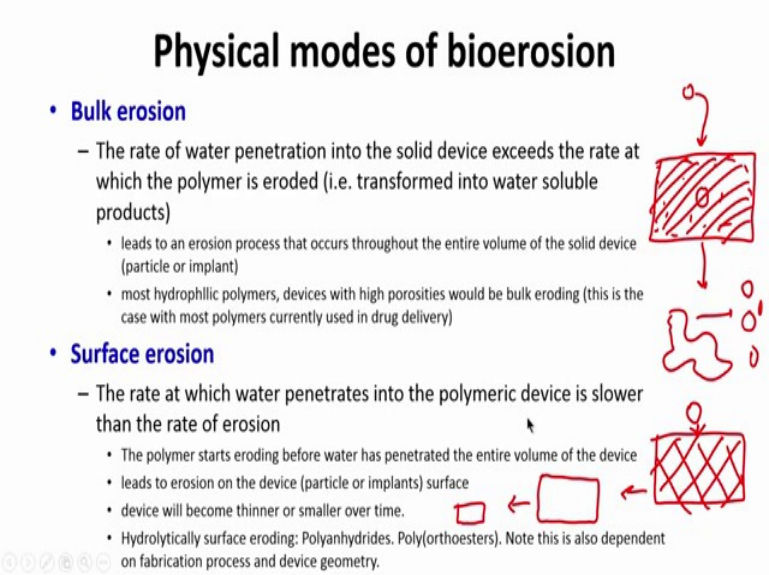

So, there are several modes of bio erosion, one is a physical mode, which could be bulk erosion. So, what do you mean by bulk erosion, is that the rate of water penetration into the solid device exceeds the rate at which the polymer is eroded.

So, what does that mean? That means, that let us say I have a device and this contains lots of polymeric chains, which can hydrolytically cleave in presence of water and the water is actually free to go in. So, a water molecule can potentially go in throughout the polymer device. Now, if this is the case and we are saying that these chains can be degraded by the water, what will happen is, that the erosion will happen throughout the matrix right, the water will go to all regions and at all regions the chains will start to break down.

So, over time this will start getting irregular in shape. So, this will become something like this, after let us say few hours and then further down it will maybe just break down into individual small units and then they will also degrade over time. So, most hydrophilic polymers are like that if they are hydrophilic of course; that means, they love water and; that means, that the water can go through in them because the water will also like them and they will be bulk eroding. There could also be surface erosion which

basically means that the rate at which the water penetrates in the polymeric device is slower than the rate of corrosion.

So, what that means, is let us say if I have a device, again containing lots and lots of polymer chains; however, the water molecule cannot go in at a rate which is faster, than at the rate which it will degrade the outer surface. So, in that case what will happen is this device is going to maintain it shape and only the edges will degrade and it will take this shape, which is again further going to take this shape and so it is going to eventually go on and on and very systematically only from the surface, it is going to keep on eroding.

So, the device will become thinner and smaller over time; however, it will more or less maintain the shape. Do you guys can think of any example you see in the real life with this? So, a good example is a soap; so, if you use soap the soap bar essentially keeps on getting thinner and smaller as you go on, it does not really disintegrates into small units. So, that is a surface erosion. Because the water is not able to penetrate inside and only from the surface the soap is eroding. Whereas, bulk erosion you see any kind of basically let us say you take a sugar molecule this the water is going to penetrate right through and then we will just completely disintegrate in your mouth ok.

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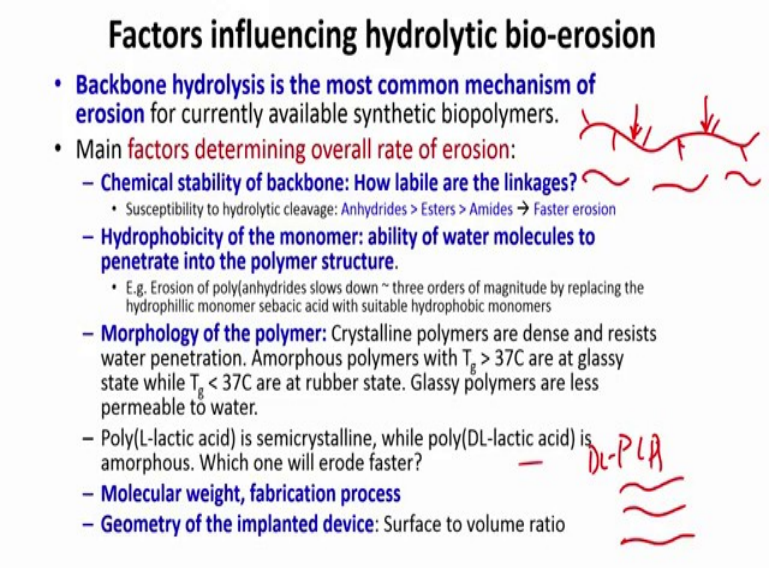

So, what are the different factors that influence hydrolytic bio erosion? So, you can have a backbone hydrolysis is the most common mechanism of erosion, typically you have a

long polymer chain and this is the backbone and there of course, side groups to it and then this particular long chain has some hydrolytic bond that is being attacked by the water molecule and eventually degrades them into smaller units.

So, and this is essentially the most common route that is used for a synthetic biopolymers. The main factors that determine the erosion is the chemical stability of the backbone of course. So, there are several functional groups that the hydrolytically cleavable such as anhydrides, esters, amides and the rate of degradation is listed here. Anhydrides degrade faster than esters which degrades faster than amides. And so, based on what the bond structures are there, what different functional groups are there the degradation will eventually change.

The hydrophobicity the monomer is also important. So, let us say if the monomer is fairly hydrophobic then the water will not try to come close to that monomer and so that would mean that the hydrolytic degradation for that is going to be slower just because the water cannot really access it. The morphology of the polymer is important, again the crystalline polymer are dense and as we said that once you are achieving a crystallinity, it is very tightly packed structure and the even the water is not able to penetrate the light is not able to penetrate. So, depending on what temperature you are using, typically at higher temperatures you will always see faster degradation; however, there are some exceptions. So, another point here is the PLA which is a semicrystalline molecule, while PDLA, which is essentially the mixed isomer of PLA is amorphous.

So, which one would degrade faster of course, the one that is amorphous, will degrade faster just because the chains are more separated out in the DL form, compared to just the PLA in the L form. And of course, the molecular weight of the chain, what is the fabrication process you have used, the geometry of the implanted device, how much surface area is there, surface to volume ratio all of this will in fact, influence your hydrolytic bioerosion. So, we will stop right here for today and we will continue with more of these biomedical polymer properties in the next class.

Thank you.