Introduction to Biomaterials

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Module No. # 01

Lecture No. # 32

Biodegradable polymers

In this lecture, we will learn about biodegradable polymers. We have learnt, what is the importance of the biodegradable polymers, in the earlier lectures.

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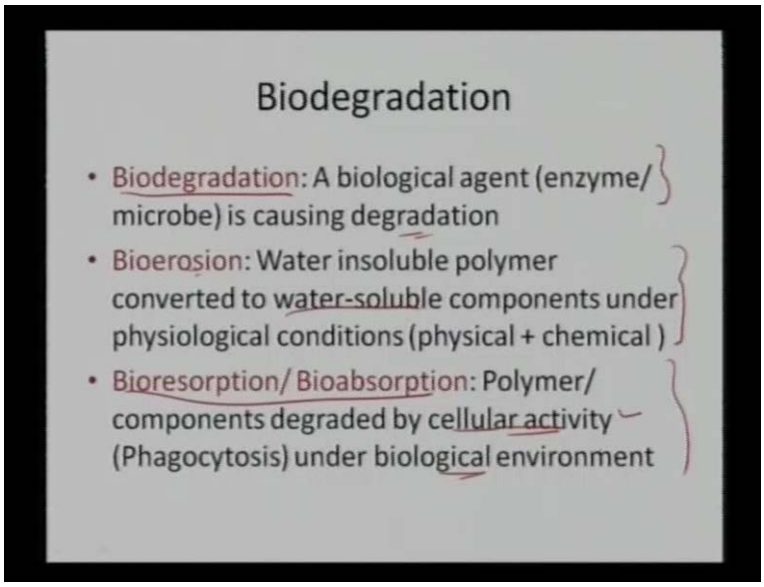

So, in this particular lecture, we will concentrate on, what are the biodegradable polymers which are currently available, and as well, we have also learnt about the biodegradation part, that, what are the different terminologies that have been basically, utilized by the engineers and scientists, to describe the degradation part. So, one can be biodegradation; that is, that requires basically, an enzymatic activity, or a microbe activity, to cause a degradation; or, it can also be bioerosion, in which case, the bio ((no audio)) in a combination of physical plus chemical activity, to cause a degradation of a

particular polymer; or, otherwise, it can also be bioresorption, or bioabsorption, in which the components is basically, being degraded by the cellular activity, such as Phagocytosis. So, in this case, we, we can see, it is the biodegradation, it is either by enzyme, or microbe; bioerosion is basically be ((no audio)) component, or it can again, be the breaking of the overall chain by a certain cellular activity, that is being called as a bioresorption, or the bioabsorption. And, all these things are happening within certain biological environment. So, those are the other terminologies which we have utilized earlier, in terms of defining the biodegradation. And, at, earlier, the, first of all, the developments which have been initially, the way it was started, in terms of defining materials, it started all with defining certain stable materials.

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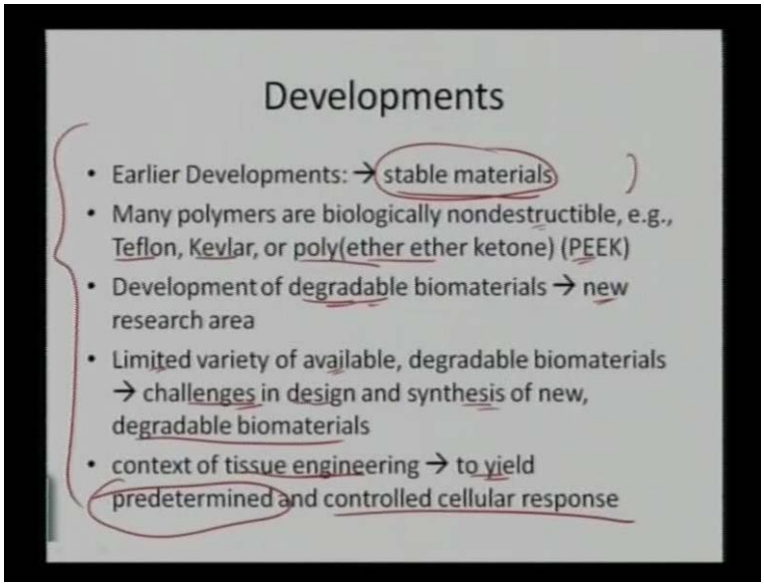

Because, once we are implanting something, something into the body, probably, we learnt that, probably, we need to have some materials, which is stable under extreme, extreme environment, which is the body fluid environment and it should be able to sustain there for a very, very prolonged time; that was the earlier mentality. But later on, later on, now, we have realized that, that particular material, can also impart certain functionality; it can, it can allow the precipitation of a new, new cells, or new bone around the damaged area. So, recently, the focus has also been on developing certain biomaterials. So, earlier developments were basically on exploring the stable materials and there are many, many polymers which are available, which are highly stable under the biologically, biological environment; and, they are virtually non-destructible. Certain

examples are Teflon, Kevlar, or poly (ether ether ketones) PEEK. So, there are certain materials such as Teflon, Kevlar and poly ether ether ketone, which are basically, very very stable for a prolonged duration of time, even under severe biological, biological conditions. So, they become generally, non-destructible.

So, recently, this term of degradation, or the degradable polymers has come into the picture; because, we can impart certain functionality without causing any (( )) effects to the bone. In case we have material, which has been implanted permanently into the body and which does not degrade at all, which remains there for a prolonged time, that will cause certain, the shielding of, the stress shielding and in the process, the new bone formation will basically, be hindered. So, in that case, we want the material to get dissolved into the body, so that, that functionality can be taken up by the new forming bone, and the bone really stays there for a, new bone really starts growing in the damaged area. So, that is the reason, the research has been not targeted more on developing of certain degradable, degradable materials. And again, there is only a limited research has been done, so, we have only limited number of available degradable materials.

Why that is there because, it requires (( )) design first of all. As soon as the material is being implanted into the body, and it is a degradable polymer, first challenge is the design part, because how the dissolution will affect the overall integrity of the structure in entirety. So, if I, if I am implanting certain biodegradable polymer, and with time, it starts to dissolve; then, we need to know the exact mechanism, of how it is dissolving, and exact time, when it will get dissolved. So, for that, it requires certain challenges in design, in terms of synthesizing new degradable biomaterials. And, at the same time, it is very, very important, in terms of the tissue engineering as well. Because, once, once a material is implanted, it has to be taken over by certain tissues, the healthy tissues which can reduce the overall damaged area. So, in that particular case, we need to have a particular material which is properly designed, or properly engineered, to yield a controlled cellular response; and, that also can be, should be pre-determinable. So, we, we need to develop certain material, which can have a predetermined dissolution rate, and as well as the, cellular or the tissue engineering or the cellular response rate, as soon as the material is getting dissolved.

So, that is what we can see, in terms of development. The early development was done basically, on stable materials, and we have certain, many, many materials which are available, which are highly resistant to the biological attack; those are polyether ether ketone, Teflon, Kevlar and many other. And again, the development of the degradable biomaterials, that is a new research area, because, it requires so many technicalities, in terms of designing the material, in terms of determining their dissolution rate and again, in terms of the controlled cellular response, how the cells will respond to the particular implanted degradable polymer.

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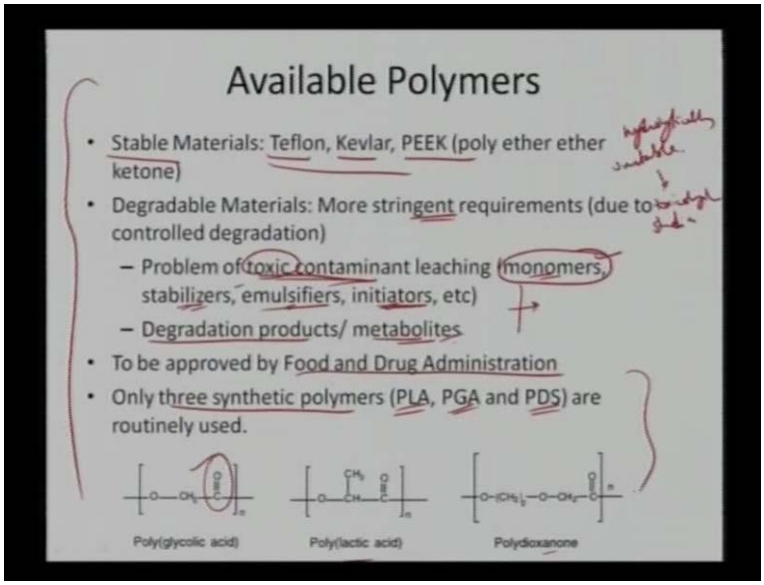

So, it introduces much more of a complexity, in terms of designing these degradable polymers, and that is how the new research is basically being targeted onto. And, as we discussed that, there are certain stable materials which are Teflon, Kevlar, PEEK, which have been basically available; but over the past decade, there has been much more research on dissolvable biomaterials, which can basically, be dissolved hydrolytically. So, we have some hydrolytically unstable material, hydrolytically unstable material, that can basically degrade and then, we can perform some toxicological studies on them. And then, we can basically, develop certain new materials, which can perform, which can define, decide the mechanism of the dissolution; we can decide the overall temporal stability, at what rate they will dissolve, and what is the cellular response to that particular, developed new biomaterial. So, those are the certain complexities, which we need to basically, develop. And therefore, there are many, many stringent requirements

on to them. So, they can come up, in terms of toxic contamination; in case, one material, one polymer is getting degraded, it should not, it should not render any toxic, toxic ingredients into the body. So, while leaching, it should be, become monomer and it should be, basically get stabilized; it can also form some emulsifiers, initiators. So, there are many, many entities, which basically comprise polymers such as monomers, stabilizers, emulsifiers or initiators, which are made to, made to engineer a particular polymer, in terms of making it biodegradable. So, we need certain stabilizers, so, that, that keep the material stabilized enough, for a long time; emulsifiers, initiators to initiate the particular reaction, or the polymerization.

So, there are many, many ingredients, which are they in a engineered polymeric material. And once they have been degraded into the body, they should be free of toxic excretion. So, that is what is being the, one of the challenges, which we can really get. And again, the degradation products, or metabolites, which are there in a polymer, they should not again be contaminating, and they should not cause any adverse effects to the body, or to themselves. That is again, one more challenging requirement for engineering a degradable material.

And again, after that, all that, it needs to undergo certain clinical, in vitro, first of all, in vitro studies, that basically confirm, that the material is biocompatible, or cyto-compatible. Then again, it has to undergo certain in vivo studies, and then, it should be, also undergo clinical trials; and then, again, phase 1, phase 2 types of clinical trials. And then, it has to be approved by Food and Drug Administration. So, there are so many stringent requirements, that whatever materials which have been developed earlier, they continue to be the dominating biodegradable polymers. Because, it, there is so, there are so many impositions, like first of all, materials take very stringent requirements of design, then, control, and then, again, through in vitro, in vivo, and then, clinical trials; it is such a lengthy and complicated process, and again, there are certain stringent requirements that they have to possess so and so, in terms of mechanical, in terms of biological criteria.

So, they, they had, there are very stringent requirements, which have been imposed by the Food and Drug Administration. So, currently, basically, there are only three synthetic polymers, which are currently, or which are very routinely used. And, it becomes very hard to develop certain new biomaterials, though we have other biomaterials. But, the

exact, proven clinical cyto-compatibility is, I think, still under investigation. So, we have poly lactic acid, poly glycolic acid, and polydioxanone. So, this is the overall structure of the poly glycolic acid; it is again a ketone and again, we have, it is an C O O H bond. So, we, we have a poly glycolic acid. And then, again, we have a poly lactic acid and then, we have polydioxanone. So, these are certain available polymers, which are routinely used in the, as the biodegradable polymers. So, we have certain stable polymers of, such as Teflon, Kevlar, and PEEK. And then, we can, in terms of developing a degradable bio materials, they they have to undergo very stringent requirements of, basically being, possess good ingredients, such as the toxic contaminant should be absent, while the material is being leached out; so, even the monomers, stabilizers, emulsifiers, so, even the initiators, they have to be free from any toxic ingredient. Then, the degradation part of it also should make it much more stable; even the metabolite should not be toxic.

And, they have to be approved, after the in vitro studies, in vivo studies, and again by the clinical trials, to make it approved by the Food and Drug Administration. And currently, there are only three polymers, which are basically being routinely used. So, poly lactic acid, poly glycolic acid, and polydioxanone. Why, because, initially when the development has occurred, these materials have come out, come out as one of the established practices of utilizing all these three materials as biodegradable polymers, in such sutures, or may be a wound closure. So, they have retained as one of the primary users, because it has now become so difficult, to get the new biomaterial approved by the Food and Drug Administration, in terms of undergoing stringent design and all such requirements. And currently, there are many, many materials which are available, the polymeric biodegradable material which are available.

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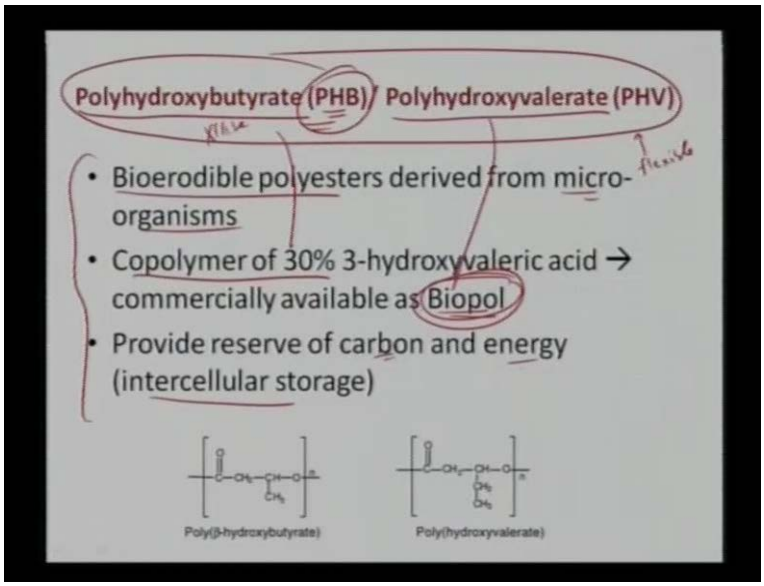

So, first of all, one is polyhydroxybutyrate, which is also called PHB, or polyhydroxyvalerate. And again, these are bioerodible polyesters; it means, they, they basically, are getting, they are basically being converted from the biosoluble form to, bio insoluble, water insoluble form to the water soluble form, after undergoing certain microbial activity. And, then again, they are derived from the microorganisms. So, the, that is what the, that is what these polymers are, polyhydroxybutyrate. And again, the copolymer of 30 percent 3 hydroxyvaleric acid and rest polyhydroxybutyrate, it is now commercially available as a polymer, biodegradable polymer which is called Biopol. And, they also serve as a intercellular storage, basically, because they have excess in energy and carbon available with them. So, that is how they are basically being utilized as biodegradable polymers. So, in this case, we can see that, it is…And again, the PHB is one of the crystalline materials and it is little brittle in nature, whereas, the combination of polyhydroxyvalerate and polyhydroxybutyrate, so, this is more crystalline in nature. And then, this one basically acts, makes, makes it more flexible; and in this case, we can see there, there is a combination which is now available, by the co-polymerization; because it is much more crystalline; this is much more flexible. So, it is now available as a, commercially available co-polymer of, known as Biopols.

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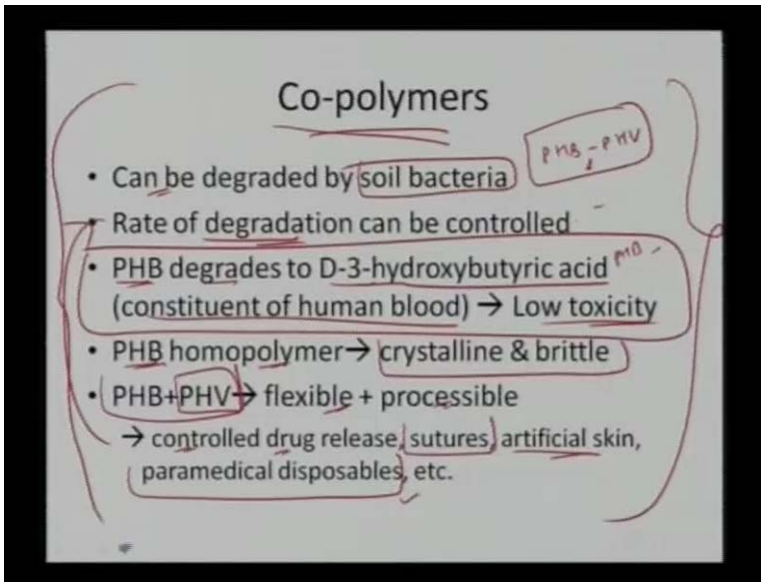

So, it is, that is what is available as here. And again, we can see that, the now, the co-polymer, it can also be degraded by the soil bacteria. So, the degradation part also is very easily attainable in this particular case. And again, by the combination of PHB and PHVs of the polyhydroxybutyrate and polyhydroxyvalerate, this polymer can be engineered in such a manner that, the degradation rate can be easily controlled. So, by a particular combination of PHB and PHV, we can control the rate of degradation and hence, we can utilize them as a controlled way of engineering a particular structural material that, as soon as this material is getting degraded, it is being taken up by the surrounding cell to retain the strength. And again, PHB is one of the, again, is one of the biocompatible copolymers; why, because, it degrades to a D 3 type hydroxybutyric acid, and which, which basically, is nothing, but a constituent of the human blood.

So, that is the reason, this PHB, it shows a very low toxicity. So, in this case, we can see that, PHB, once it is getting degraded, it is degraded, degrading to the D 3 hydroxybutyric acid and which essentially, is the constituent of human blood. And, that is the reason, it shows the low toxicity. And, as we know, as we have talked earlier that, PHB, it is, this homopolymer is much more crystalline and brittle. So, that is the reason, we want to add some flexibility, so that, we can easily process the material, and that is why we use the polyhydroxyvalerate polymer; and this copolymer is now, because, much more flexible and processible; and, because of that, once we have, once we can, now, this copolymer and if you can control the degradation rate, because, by allowing a proper

combination of PHB and PHV, we can allow easy controlled release of the drug. And now, once we can retain the strength by increasing the PHB content, because it is much more crystalline; we can also utilize in, utilize in sutures, which can sustain for little longer time. Generally, some sutures, they degrade in 2 to 3 weeks. So, in this case, if we want to retain the sutures for a little longer time, we can allow a proper combination of PHB and PHV, and somehow we can control the strength of the, those sutures, for a prolonged time.

We can also utilize them for the artificial skin, or even for paramedical disposables; so, in this, in case of certain industrial applications, we can also utilize them for some paramedical disposables. So, we can see that, copolymer becomes much more boon, in terms of controlling the drug, the drug release rate, in terms of deciding a particular combination of PHB and PHV. We can also decide the overall strength, which can be retained by the sutures for a prolonged time, or we can also utilize them as artificial skin, or also for the paramedical disposables, in case, we want to seal certain chemicals and all; and we can basically being able to dispose it, after, after its usage. So, these copolymers come as a rescuers, in terms of all such applications. So, that is the overall advantage of utilizing the PHV and PHB. PHB is the polyhydroxybutyrate, which is highly crystalline; but it is very, very brittle; that is the reason we add PHV to it, that is polyhydroxyvalerate; and by the combination of them, we can always control the overall degradation rate; and again, they can also degraded by the soil bacteria.

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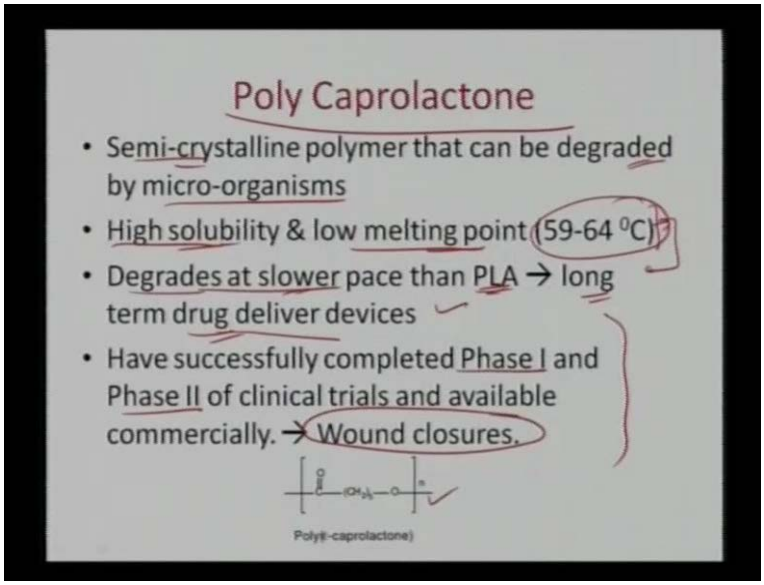

So, that is the overall thing about the PHB and PHV copolymers. The second class is the polycaprolactone. And polycaprolactone, it is a semi-crystalline polymer; like in PHV, PHB, we had much more crystallinity; in polycaprolactone, it is semi-crystalline polymer and again, it can be degraded by, by certain micro organisms. And, and, it has a very high solubility and it has a low melting point; and since it is, it is highly soluble in certain organic compounds, and it has a low melting point, it basically, eases out the processing part; that we can easily process the material. Because, once we, once we can easily solubilize, we can make a solution of this polycaprolactone; and then, we can process it at much lower temperatures, because its melting point is only 59 to 64; so, we can attain very high fluidity even at, even at, say 100 degree centigrade. And now, that makes the material very, very processible; that we can easily cast into certain shapes, we can compression mold it to any, certain complicated shape.

And again, the advantage of this one is, again that, it can degrade at a slower pace than PLA; and, so that, we can device certain drug delivery systems, which can sustain for a much longer time. So, if you have polycaprolactone, we can design the drug release rate in such a manner that, the drug release rate can be particularly controlled, but the system will remain in the body for a prolonged time, because, it has a low degradation rate than that of a PLA. So, again, there are certain clinical trials, which have already been done, phase one and phase two, and they are now commercially available. And, they are mainly utilized for the wound closures as well. So, this is the overall structure of polycaprolactone; that, these are the semi-crystalline polymers and because of their high solubility and low melting point, they become highly processible; but because of its lower, lower degradation rate, in comparison to that of a PLA, or the polylactic acid, we can induce certain long term drug delivery devices into the body, and now, they can, they can, they can render the drug, for a very long duration of time, in case, we need a extended drug delivery, drug release, in certain cases. We can basically attain that, using polycaprolactone. And, they have successfully completed the phase one and phase two, easily. So, that is what is being basically, being utilized for the Capri, the polycaprolactone out here.

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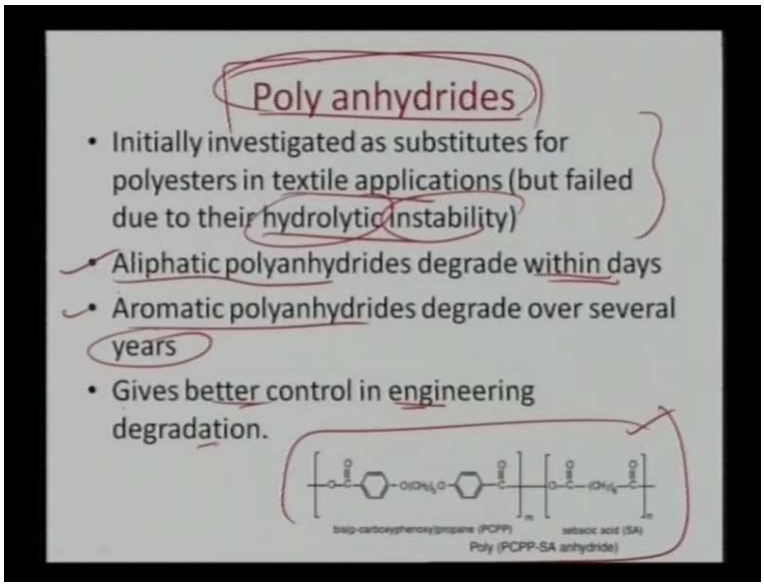

And again, there are certain second classes of material, and then which are, which are called polyanhydrides. And again, initially, polyanhydrides, they were, once they were being developed, they were being developed for substitute in the text, for the textile applications. So, that is what the initial exploration of this polyanhydrides had started; that, they were being substituted for the polyesters, so that, they, they can make out a new textile material out of this polyanhydrides. But, eventually, with time, they, they, they have failed, because, they have low stability, low hydrolytic, hydrolytic stability and so, they become highly instable in presence of hydrolytic, hydrolytic conditions. So, they basically had failed as, as a textile material, or as a replacement for the polyester. But now, eventually, that started, or triggered the development of this polyanhydrides as a bioabsorbable, or the biodegradable materials.

And again, we can see that, the polyanhydrides, they are very specific, in terms that, the aliphatic polyanhydrides, they can degrade within days; whereas, the aromatic polyanhydrides, they degrade over several years. So, we can see, so, we can see that, we have a certain window available with us; that aliphatic polyanhydrides, they will degrade within couple of days; whereas, we have aromatic polyanhydrides; they will degrade within certain, or over, over several years. So, we can develop, or decide a particular range, in which we can use this materials, as a degradable materials in terms of certain healing. So, if you have certain wounds and all that, we can always decide a particular scaffold, which will degrade slowly, or at a rapid rate. So, depending on how severe that

particular injury is, we can always devise a combination of this polyanhydrides, whether we want them to degrade either in days, or in years. So, now, this gives a better control, in terms of engineering this particular degradation.

So, we can see that, we have certain anhydrides which are available with us commercially, which are called poly PCPP-SA anhydrides. So, we have very complicated anhydrides which are available with us. So, this, this can be either aliphatic, or this can again be aromatic; so, which can, through which we can really control the overall degradation which can, which is happening on the anhydrides. And, as we know that, this anhydrides were developing being as a replacement for polyesters, so that, they can use in textile industry; but, because of their low stability under hydrolytic conditions, so, they became highly unstable, or they have failed as, to emerge as a replacement material for the polyesters; but now, they have been ventured into developing certain degradable polymers. And now, we can see the degradation rate is being developed, being governed by the overall structure, or the overall manner in which the particular polyanhydrides is constructed; if they are aliphatic, they can degrade within couple of days; if they are aromatic, they, they take a couple of years, to basically degrade. And, that provides a better control, in terms of engineering this polyandhydride as a biodegradable polymer.

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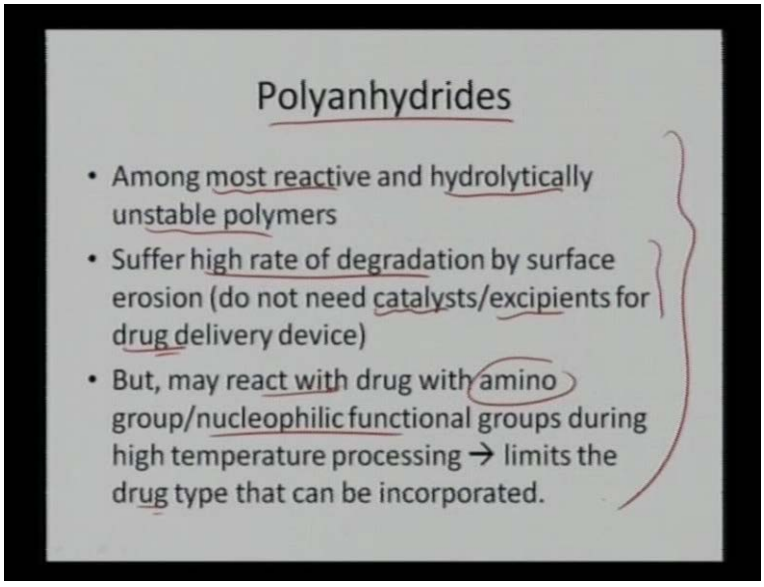

And again, the problem with that, problem with that, problem, or the advantage with this polyanhydrides is, they are among the most reactive and hydrolytically unstable polymers. So, though we say that, the polyanhydrides, they can be ranged within couple of days, to couple of years of degradation, they are one of the very, very, very reactive and hydrolytically unstable polymers. So, they have both advantages, as well as disadvantages. First of all, the advantage part, that they suffer very high rate of degradation and as, because of the surface erosion. So, they do not need any external catalysts, or excipients, for the release of the drug. So, in one case, we can induce very high rate of drug, drug drug drug release, without any external catalysts, or excipients and still, they will suffer very high rate of degradation, just by engineering the combination of aliphatic, or the aromatic polyanhydrides.

But, at the same time, because of their high reactivity, they can also start reacting with the drug itself, which is being released into the body. So, they tend to react with amino group, or nucleophilic functional group, when the material is being processed, because the processing has to be done to mix the drug with the polyanhydrides; and, the processing has to be done at little higher temperature, so that, the, it is above the melting temperature of polyanhydrides. And, during that particular process, it starts to react with the amino, or the nucleophilic functional group, and that, basically limits the drug, which can be usually incorporated with the polyanhydrides. So, we realize that, in this particular polyanhydride, we have both the advantages and disadvantages; that it is one of the most reactive and hydrolytically unstable material.

And because of that, it has the advantage that, it does not need any external excipients, or catalysts, in terms of degrading itself. So, it can easily occur by the surface erosion and it can also evolve drug delivery, without any external agents. But, at the same time, it limits the kind of drug which can be utilized in this polyanhydride, because, for high temperature processing, they tend to react with the amino, amino group, or the functional nucleophilic group of the drug itself. So, that is, that creates a problem. So, that limits the overall drug, which can be utilized with the polyanhydrides.

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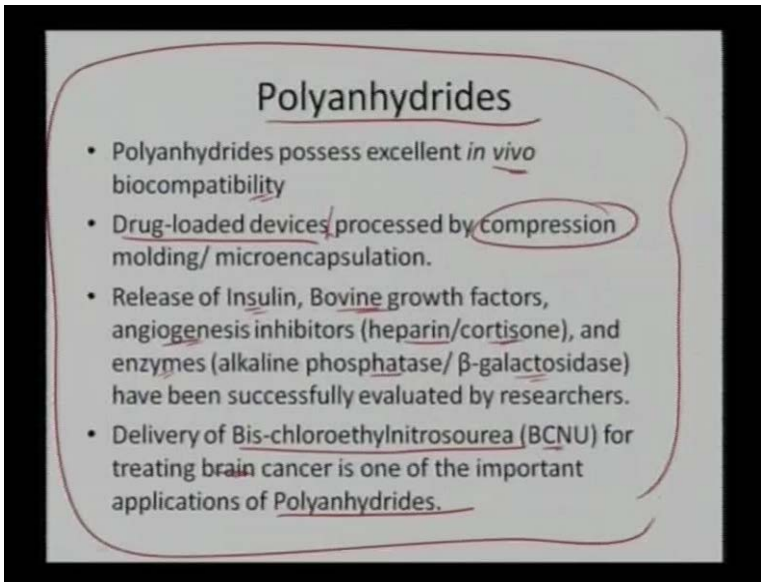

And again, polyanhydrides, they have shown to posses excellent in vivo biocompatibility, because they have the structure which is similar to, the bioproducts, or the, the breakage products of this polyanhydrides, they are not really toxic and the drug loaded devices which are, the drug loaded devices of polyanhydrides, they can be easily processed by the compression molding, or by micro encapsulation. So, we can easily process this particular materials, using certain drugs, by using compression molding, or the micro encapsulation. And again, it has shown to, shown to release either insulin, or bovine growth factors, or angiogenesis inhibitors, such as heparin, or cortisone, or certain enzymes, such as alkaline phosphate or phosphatase, or beta galactosidase, which have been successfully incorporated into the polyanhydrides and the release of this particular enzymes, or drugs, they have been successfully, being characterized, or being evaluated by the researchers. And, one of the essential application of polyanhydrides is in the brain cancer treatment; that, the delivery of this BCNU, that is Bis chloroethyl nitroso urea, which is being utilized for treating the brain, brain cancer; and, that is being, successfully being tested using this polyanhydrides. So, that is one of the very essential applications of this polyanhydrides.

So, people have seen that, (( )) seen that, polyanhydrides, they have very exceptional in vivo biocompatibility and the advantages is, polyanhydrides is, that they can be easily processed, by either compression molding, or by micro encapsulation, so that, they can be easily utilized, in terms of delivering, either the insulin, or certain enzymes, or

angiogenesis inhibitors, or they can, basically also treat the brain cancer by a release of this BCNU, particular chemical for treatment of the brain cancer. So, that is the overall advantage of this polyanhydrides, that, they have, they have, they are highly, they are hydrolytically very unstable and they were highly very reactive as well; they do not need any external agents to release the chemicals, or the drugs and they have shown exceptional, or excellent in vivo cyto-compatibility and they can be easily incorporated with certain drugs, insulins, enzymes, or the bovine growth factors, which can be easily incorporated into the polyanhydrides and they have shown controlled release rate of all these chemicals, or drugs.

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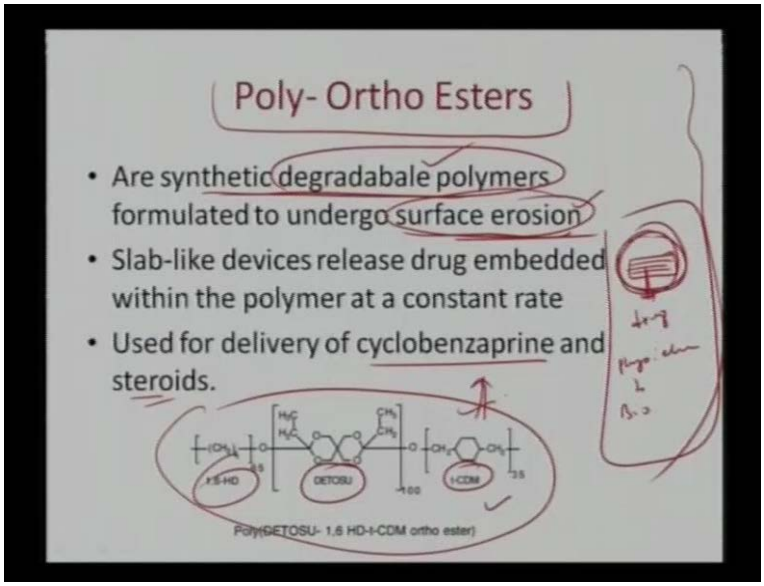

And, the next class of the biodegradable polymers is called poly-ortho esters and they are basically, the synthetic degradable polymers, which have been formulated to undergo certain surface erosion. So, in this particular case, the water insoluble, water insoluble chemical is now being converted into the water soluble product, by both chemical, as well as physiological actions, under biological conditions. And, in this particular case, a slab-like, slab-like device is basically being embedded into a particular polymer and that starts releasing the drug. So, that is now releasing the drug, at a very counter or the very controlled, or the constant rate. So, in this particular case, we have poly-ortho esters; they are synthetically degradable polymers and they undergo surface erosion.

So, the combination of both physical, as well as the chemical, chemical activity under biological conditions, it starts degrading this particular polymer, and this slab-like devices are being placed, which are embedded in the polymer and the degradation of this polymer starts releasing the drug at a very constant rate. And, they, they were basically utilized for delivery of either steroids, or cyclobenzaprine, in this particular case. So, that is what we see in the poly-ortho esters. They are degradable polymers and they have been now designed, or formulated to undergo surface erosion and now, this slab-like devices, they have been encapsulated in a polymer, which are embedded in a polymer, and that polymer degradation starts releasing the drug at a very constant and they have shown to be very good for certain steroids and cyclobenzaprine.

So, that is what the overall deal with the poly-ortho esters, that, they can provide a controlled release, controlled release of the drug at a very constant rate. So, that is the advantage with the poly-ortho esters, and here is the overall structure of the ortho esters. We can see that DETOSU 1,6 HD-t-CDM ortho esters, which are now being shown here. So, we have the DETOSU and t-CDM part here the 1,6 HD part out here. So, that is the what is being shown by the poly-ortho esters, that, they can provide a very controlled or a constant drug release rate, as the slab-like devices are being encapsulated in the, this particular polymeric material.

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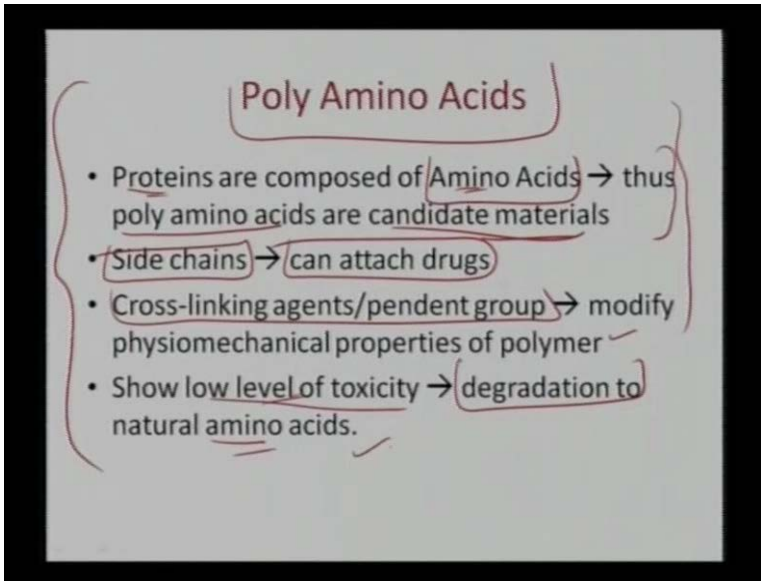

And, there are again certain other class of materials, which are also called, which are called poly amino acids; and, obviously, this also term said as pseudo poly amino acids; and, obviously, proteins have been composed of amino acids. So, the first intuition which comes out to assist, oh, why do not we use them as controlled degradable materials? So, poly amino acids, they have essentially, come out of this particular intuition, or the first action that, they are also amino acids and the degradation of this particular amino acid should not be toxic at all. So, as we know that, proteins are also made up of amino acids. So, this, this poly amino acids, or the pseudo poly amino acids, they become the candidate materials for the, for the biodegradable polymers. And, the advantage with them is that, the, again, we can have the side chains; we can always attach certain drugs to it. So, first of all, they form in the basic nature of the proteins; basic chain of proteins; it is nothing, but the amino acids and then, amino acids, we can attach some sets; on the side chains, we can always attach certain drugs; and again, on the cross linking agents, or the pendent group, we can always modify the physio-mechanical properties of the polymer.

So, depending on how do we crosslink this particular amino acid, we can always alter, or tailor the physio-mechanical properties of the polymer itself. So, on first side, on the side chains, we can always attach certain drugs, and, secondly, we can always alter the cross link properties and then, from that, we can always alter the physio-mechanical properties of polymer itself. So, we have both the advantages of either altering the mechanical properties, or altering the chemical properties, which are required for the drug delivery. So, the overall combination of these two can result, a very nice combination; that is what being utilizes the, for the poly, for the poly amino acids. And again, for, them being the basic chain of the proteins, they show a very low level of toxicity; because the degradation is to the natural amino acids.

So, that is the advantage with the poly amino acids, that, first of all, the overall philosophy is that, proteins, they are made up of amino acids; and then, now, these amino acids, they basically become the first users, first thought basically comes is that, this amino acids, now can become inherent part of the protein itself; and, they can degrade to a very non toxic ingredients. And again, on the side chains, we can always attach certain drugs; at the same time, we can, we, at the same time, we can play with the cross linking and then, we can again, define the physio-mechanical properties of polymer itself. And

again, the degradation of this poly amino acid can be, to the, can become, to the natural amino acids and then, they can show a very low level of toxicities; that is the advantage with the poly amino acids.

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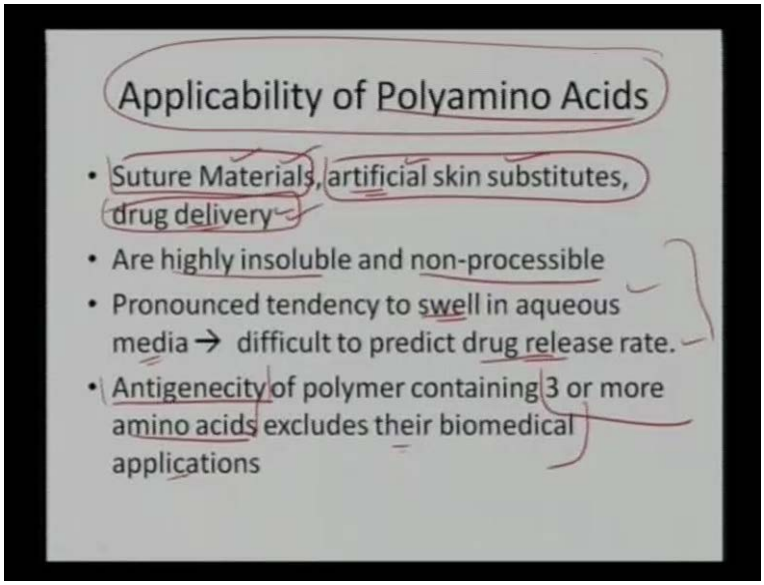

Again, the applicability of poly amino acids, it has been to suture materials; it can also provide artificial skin substitutes, or drug delivery. The advantage with the poly amino acids, it is once, since we can play with the mechanical property, or the physio-mechanical properties, we can, we can basically, design a suture, which can sustain its mechanical strength for little longer time; upto the time, at which we want it to retain. Generally, sutures, they are highly degradable and they tend to degrade within very short time. So, that is the advantage with the poly, pseudo poly amino acid that, we can design certain suture material, which can sustain the strength for a little longer time; they can also be utilized as the artificial skin substitutes. So, in that particular case, we want the strength, or the degradation to occur as soon as the new skin is developing. Again the, we can also provide a controlled drug delivery using this poly amino acids, deciding on its, either the drug, on the drug part from the side chains, or the physio-mechanical properties of utilizing the cross linking. And again, they are highly insoluble, but the problem with them is, they are highly insoluble in organic compounds and again, they become also non-processible. And again, they have problems of that, that they tend to swell a lot in an aqueous media. And, once they are swelling, it becomes hard to basically interpret, what will be their overall dissolution rate, or a drug release rate.

So, that is the problem with them that, they are highly insoluble and again, they have, they, that makes them non-processible; not, they do not, they do not become easily processible; and again, they have the tendency to swell, once they come in contact with aqueous media; and once they swell, then, it becomes very hard to predict, what will be the overall drug release rate, in the poly amino acid; that has basically limited the overall applicability of this poly amino acids. And again, they, it has one more, one more problem that, that in case, we have 3 or, because of the cause of antigenecity of this poly amino acid, when, when it contains three or more types of amino acids; so, that basically excludes them as a potential, for the potential biomedical applications. So, though they have been used as a suture material, artificial skin substrate, or a drug delivery, their antigenecity, when we have amino acids of 3 or more being contained by the polymer, so, that creates a problem in terms of an antigenecity. And, that basically exclude their biomedical application. Again, they, they do not have any controlled drug release rate, because, they tend to swell; and once they are swollen, it becomes hard to predict the overall degradation rate and that basically, limits the overall predictability in terms of characterizing, or quantifying what will be the overall drug release into the body. And again, their insolubility and, and the non-processibility, it basically has limited the overall application of poly amino acid as the biodegradable polymers.

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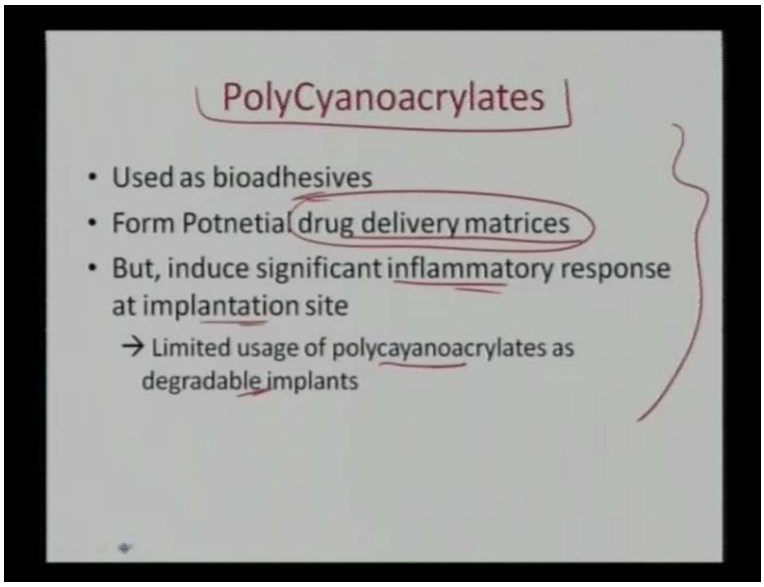

The next class of biodegradable polymers is the polycyanoacrylates and they have been basically utilized as bioadhesives, and because, they form potential drug delivery

matrices. But again, they have problem that, they tend to induce a significant inflammatory response, once they were implanted. So, they tend to create some inflammation at the implantation site; and that is basically, limited the use of poly, polycyanoacrylates as a degradable implants. So, though polycyanoacrylates have been utilized as bioadhesives, they tend to basically cause inflammation at the implantation, implantation site and they tend to form very potential drug delivery matrices, but because of inflammation, their overall usage has been limited in, in the, limited as a biodegradable implant.

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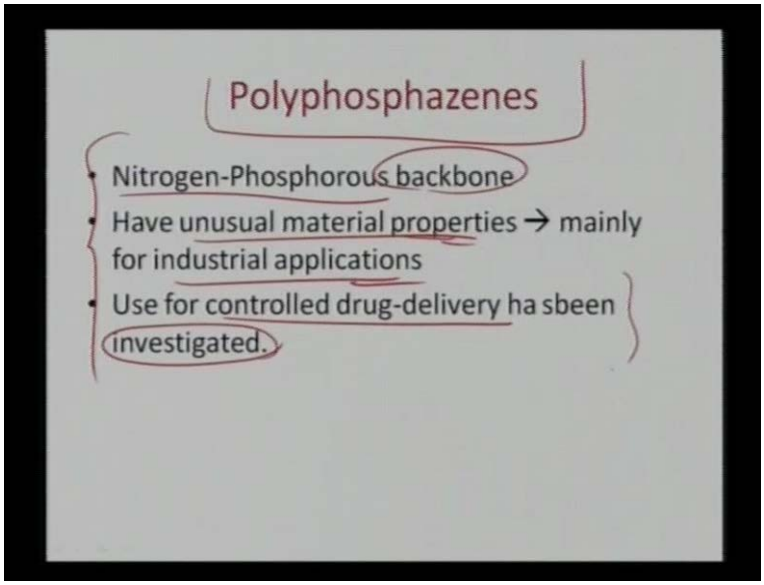

Then again, there is a next class of biodegradable polymers which is polyphosphazenes, and again, this is made up of the Nitrogen Phosphorous bond and those form the overall backbone of this particular polymer; and, they generally have very unusual material properties; and, they tend to be mainly utilized for the industrial applications. Their use for serving as a controlled drug delivery has also been investigated; but again, they, they do not tend to show such straight forward results. So, in this particular case, they show very unusual material properties, though they, they have very different material properties in comparison to others, which we will see, in case, later on. So, we can see then, they found the nitrogen phosphorous bond basically, formed the backbone and they are mainly utilized for the controlled drug delivery and, but they were mainly utilized for the industrial application; not really as a biodegradable polymers in, into the body.

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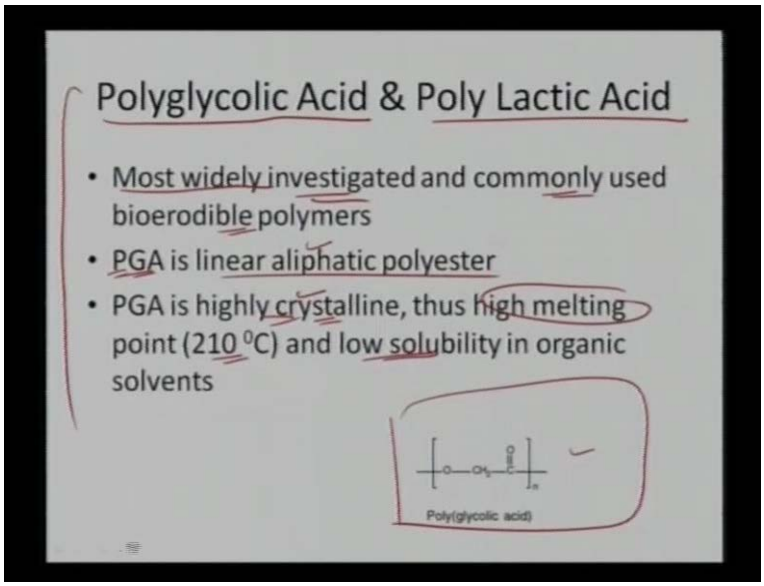

And, this is one of the very important classes of the biomaterials, which is called poly glycolic acid and the poly lactic acid. This is one of the very initial synthetic polymers which have been developed and now, they have been retained as the, one of the primary biodegradable polymers, which have been utilized very, very widely. And again, as we see that, they are most widely investigated, as well as they are most commonly used as a bioerodible polymers. And again, we see that, the PGA is a linear aliphatic polyester and because of its linearity and aliphatic, aliphatic nature, it is highly crystalline, which actually increases its melting point to very high, 210 degree centigrade; and because of its high crystallinity, its solubility is also very, very low in the organic solvents.

So, we can see that, initial development, which was there for the stable materials, these are one of the first class of material which were biodegradable in nature, and after their approval, it has become very hard, because these materials are so good, that, they have imposed very stringent requirements of biodegradation, as serving as a biodegradable polymers into the body. So, there are only three very widely used polymers, which are poly glycolic acid, poly lactic acid and the polydioxanone, and among them, poly glycolic acid and poly lactic acid are one of the most commonly used bioerodible polymers. And again, PGA is a linear aliphatic polyester, as we see here. This is the (( )) poly glycolic acid, what we see here; and again, it is very crystalline, crystalline in nature and thus, it has a very high melting point of 210 degree centigrade; but it has a problem that, it possesses low solubility in organic solvents. So, that actually creates a problem, in

terms of processing it, because we need the material to be highly soluble in a particular organic solvent, so, we can cast it into certain difficult shapes.

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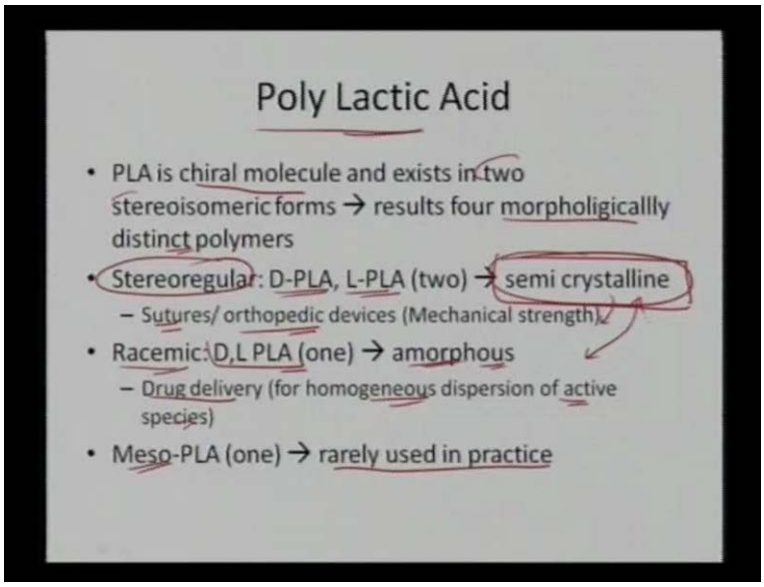

But, PGA is very crystalline and that makes it also a little more brittle. And again, we see that, the, on the other hand, the poly lactic acid, poly lactic acid is a chiral molecule, and it basically occurs in two stereo-isomeric forms, which is basically, form two into two, four morphologically distinct polymers. One can be stereo-regular; it has two forms, which can be D-PLA, or L-PLA; and, they are semi-crystalline in nature. It can be racemic, which is D comma L-PLA, this, which is much more amorphous; and it can also be meso-PLA, which is being rarely used in practice. And now, coming to their overall properties that, since the stereo-regular, the D-PLA and that L-PLA, since it is semi-crystalline in nature, it has a good mechanical strength and because of good mechanical strength, it is, it is utilized in sutures, or orthopedic devices.

On the other hand, the D comma L-PLA, it is amorphous in nature. So, it can be utilized as the media for dispersing active species or drugs, for drug delivery. So, that is what we can see that, PLA, because of its different stereo-isomeric forms, it can form four, four morphologically distinct polymers, and depending on its overall structure, like stereo-regular, it is much more semi-crystalline in nature. So, it can provide high mechanical strength, and because of high mechanical strength, it can be utilized as either the sutures, or orthopedic devices, either as bone screws, which can impart much high, or better

mechanical strength, or it can also be racemic, in terms of D comma L-PLA, and because of that, it can, it can serve as a matrix for the dispersion of the active species of the drug, so that, it can always release drugs very easily. So, that is how the overall, in overall engineering has been done for this poly lactic acid, depending on the overall mechanical properties, it can be either semi-crystalline, or amorphous, and based on that, the overall degradation of poly lactic acid can be controlled, in terms of serving a particular functionality, which can be either sutures, orthopedic devices, or even be drug delivery release.

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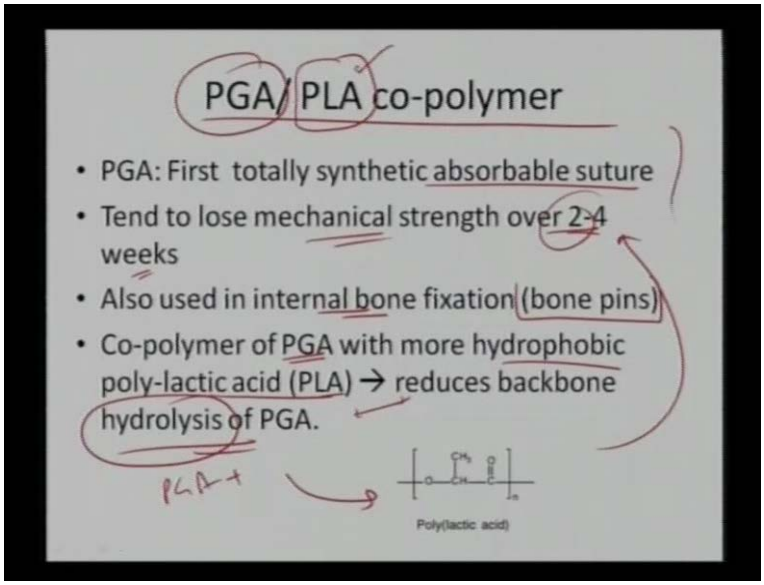

But again, the combination of PGA and PLA, it is one of the totally synthetic absorbable suture; and, the problem with that is, it tends to lose its mechanical strength over 2 to 4 weeks. So, it basically degrades very quickly and it can also be used in the internal bone fixation, when we require a very low durations. So, it is basically being utilized as the bone pin. And again, this particular copolymer is basically being utilized as a combination of PGA and PLA, and again PGA has, has a low, lower mechanical strength of 2 to 4 weeks. So, to basically conquer that, the PGA will basically dissolve in 2 to 4 weeks; that is the reason we add PLA to it, because PLA is much more hydrophobic in nature. So, copolymer of PGA, it combines to the hydrophobic poly lactic acid and that reduces the overall hydrolysis of PGA. So, we have PGA; it comes in combination of poly lactic acid, which is much more hydrophobic, and that reduces the overall damage, which is caused by the hydrolysis of PGA. So, the overall dissolution can be much

enhanced by, by more than 2 to 4 weeks. So, PGA tends to dissolve in 2 to 4 weeks and that can be, being conquered by adding much more super hydrophobic PLA, and that basically sustains the overall, or basically hinders, or restricts the hydrolysis of PGA.

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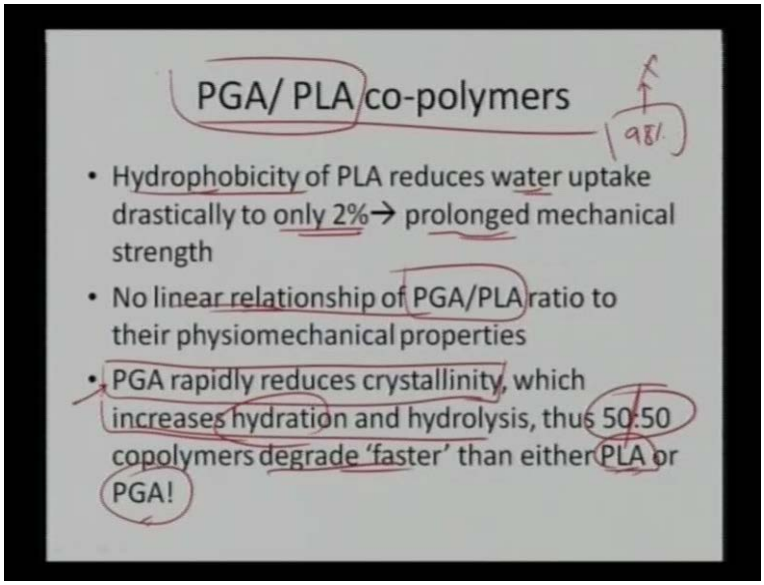

So, that is the one of the first developed, basically copolymer, which can, which is much more biodegradable. And again, to appreciate the overall strengthening, or the prolonged mechanical strength, with the addition of PLA into the PGA matrix, we can see the hydrophobicity of PLA is so strong, that it will reduce the water uptake of the thin film, which is being developed on the PGA PLA, by only 2 percent. So, the 98 percent of water is being basically not taken, or being discarded. So, with the addition of PLA, only 2 percent water uptake occurs for PGA, for its hydrolysis. So, now, we can see the overall strength, or the mechanical strength, has now basically increased, or it has prolonged in time as well. So, overall mechanical strength is now sustained, for a prolonged duration of time; but at the same time, there is no linear relationship of how PGA PLA will interact, and that will provide certain mechanical properties, or physio-mechanical properties. There is no direct relationship between the PGA PLA ratio, which can easily predict the overall dissolution rate of this degradable polymer.

But again, again, we can see that, PGA rapidly reduces, reduces crystallinity. So, dissolution of PGA will basically tend to reduce the crystallinity, and which will increase the hydration and hydrolysis. So, so, basically, we can see that, the dissolution of PGA

will again reduce the crystallinity, and which will start introducing much more hydration and hydrolysis. So, people have seen that, a 50-50 combination of PLA PGA, basically degrades much faster than either PLA, or PGA. So, the presence of PGA causes much more reduction in the crystallinity, and which again increases the hydration and the hydrolysis, the loss of PGA; so, it is much more faster, when we have 50 percent PGA. So, the 50-50 copolymer will degrade much faster than either PLA, or PGA; that is one of the beauties of this PGA PLA, that the combination of this can be engineered in terms of rendering a biodegradable polymer, which can dissolve at much faster rate.

So, either we can control the overall hydrolysis by adding much more of PLA, which is hydrophobic in nature, that reduces the water intake, or we can increase the PGA content in turn, so that, we can, we can somehow engineer a particular degradation copolymer, which can degrade at much faster than, faster rate than either of PLA, or PGA. So, that is the advantage of this, utilizing this PGA PLA copolymer. So, we can have a degradation of PGA, which can be either be 2-4 weeks, which can again enhance it, by the addition of PLA, to much, to much larger, larger prolonged time, or it can be even shortened by a particular combination of PLA and PGA, to much shorter duration, so that, that material can degrade at much faster rate, than either of PGA, or PLA.

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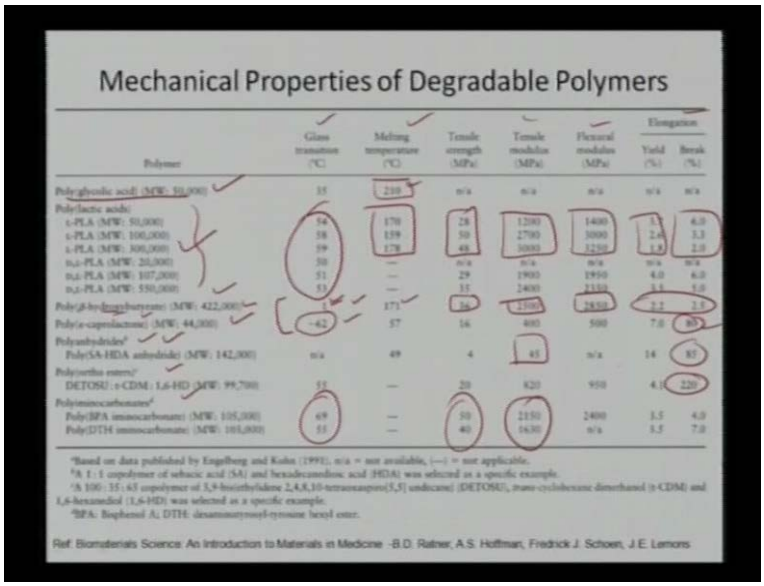

Now, there are certain mechanical properties out here. So, that part we can see, that we have this poly glycolic acid, because of its aliphatic nature, we saw that, it has a very

high melting point, and because of that, it is again, tends to be very, very crystalline in nature; at the overall processing part also, becomes much more difficult for poly glycolic acid; and again, it has a low solubility in organic solvent; so, that makes the processing very, very difficult. Then, we have different classes of poly lactic acids. So, again, we can see the overall glass transition temperature, in which we can make it work above this temperature; it is around 50-60 degree centigrade. And again, the melting point is little lower than that of a poly glycolic acid. Its strength is also couple of mega Pascals, from 20 to 50 mega Pascals. They have tensile modulus in the order of couple of giga Pascals, 1to 3 giga Pascals and they posses high flexural modulus, in terms, it has a much more flexibility. So, that is basically, that it can provide a much more good elongation, in terms of fracture.

And then, we have again, PH PH polyhydroxybutyrate, PHB. Again, we can see that, they, it has very low glass transition temperature. So, it can be easily worked very easily. It has a melting temperature of 171; a tensile strength, again, approximately 36 mpa; and again, it has a very high tensile modulus; but at the same time, it possesses very high flexural modulus as well and it can, it provides a generic yield and the break percent elongation. And again, with the polycaprolactone, it has a glass transition of minus 62, which makes it very, very brittle even at room temperature, because, it makes it very, very flexible at, flexible at room temperature. So, that is the advantage of this, the caprolactone that, the glass transition temperature is below the room temperature. So, at room temperature, it is very, very flexible. It is the same, same case is with, with the polyhydroxybutyrate; the glass transition temperature is much more lower. So, at temperatures higher than the glass transition, makes the, makes the polymer much more flexible.

So, in this case, the materials are very, very flexible, as you see. And again, the break percentage is very, very high; the elongation percent is very high. And again, the polyanhydrides, they also show very high percent elongation, as well as the poly-ortho esters; whereas, the poly amino, poly amino carbonates, they show a glass transition of 55-69; tensile strength is 40-50 mega Pascals, whereas, the tensile modulus is again couple of giga Pascals and we can see the polyanhydrides, they possess the, one of the very low tensile modulus; they are very, very flexible in nature, as we see here. So, that is the overall deal with the mechanical properties of the, of the degradable polymers,

starting from poly glycolic acid, poly lactic acids, polyhydroxybutyrates, polycaprolactones, polyanhydrides, or poly-ortho esters and the poly, poly amino carbonates. So, that is the overall generic properties of the materials starting from glass transition, melting temperature, their elongation, flexural and tensile modulus and the tensile strength.

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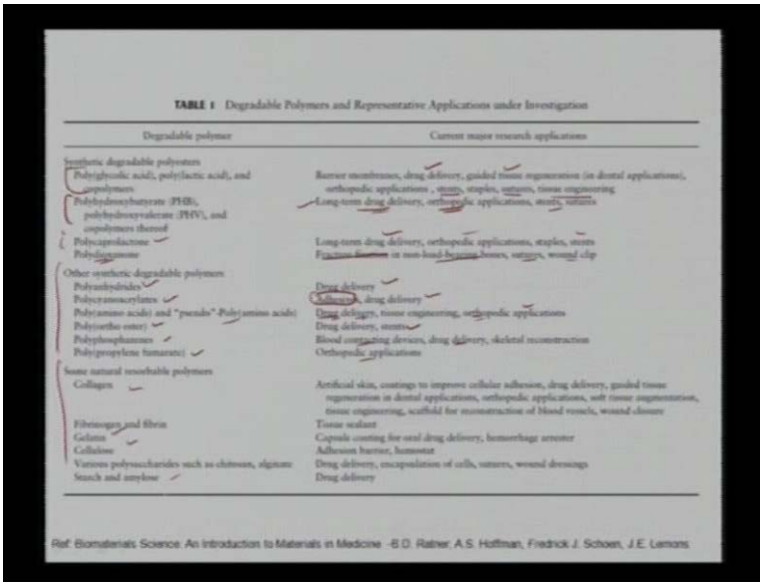

And again, coming to the overall applicability part, we can see that, the synthetic degradable polymers, in terms of poly lactic acid and poly glycolic acid, they have been widely utilized in the drug delivery, or the guided tissue reengineering, basically for the dental applications, as sutures, as staples, stents, and also in the tissue, tissue engineering. There is a combination of polyhydroxybutyrate in the poly, polyoxyvalerate. They have been utilized for the long term the drug delivery, delivery, because, depending on, depending on the combination PHB and PHV, they can provide very long term drug delivery in comparison to that of PLA; and they have been also utilized for the orthopedic applications, for stents and sutures. And again, coming to the polycaprolactone and polydioxanone, polydioxanone is again, one of the very, very, very much utilized biodegradable polymer. It is basically utilized for fracture fixation in non-load bearing bones, or sutures of bone clips. For polycaprolactone, it is being utilized for the drug delivery, or staples, stents in orthopedic applications. And, there are certain other synthetic degradable polymers such as polyanhydrides, for drug delivery; poly, polycyanoacrylates for the adhesives, mainly utilized as adhesives of drug delivery; and

poly amino acids are, are called pseudo poly, pseudo amino acids, for drug delivery and orthopedic applications; but as we know that, because of the swelling, they tend to, have a very uncontrolled drug delivery rate. So, that is the problem with them.

And again, they they have very different...So, that, so, that is the problem with them that, they have, first of all, they, on swelling, they do not really tend to give up a particular drug delivery; and also, they, they tend to a, because of their anti, because of their antigenecity, and because of their insoluble, insoluble nature, they are, basically are limited by the application. And then, we have poly-ortho esters; because they can be utilized for the drug delivery of the stents; polyphosphazenes, they have been utilized for the blood contacting devices, drug delivery, or polypropylene fumarates for orthopedic applications. And, there are other, certain, some natural dissolvable polymers as well available, which can extend from gelatin, cellulose, collagens, starch and amylase, basically for various applications.

So, in the overall, we can see, there are variety of polymers, which are available, which can be again controlled by a particular combination, by making a copolymer, and that can be utilized for the drug delivery devices of a certain wound healing applications. And also, depending on the mechanical property, or physiochemical properties, they can be easily tailored depending, depending on what kind of copolymer, which can devise. And, in comparison to the long term non-interacting polymers, they, the biodegradable polymers, they have to undergo very stringent requirements. Because, first of all, the design part, they have to be designed properly, so that, upon degradation, they do not really lose their overall structural integrity; and they, their overall release rate, or the overall cellular response also has to be tested; and, it has to be predetermined, or pre-estimatable, that upon certain, and certain degradation rate, that will be the overall cell response; otherwise, it will lose the overall integrity with the surrounding tissues.

So, that, the, there are certain issues, which are basically related with that. So, they have to be, first of all, in vitro tested, in vivo, particularly established on animals, and there have to be certain clinical trials, before it can be easily commercialized. That is the overall deal with the bio, biodegradable polymers. They have to be, they have to be, undergo very stringent requirements of the Food and Drug Administration and then only, they can be commercially established. And, depending on their applicability, PLA and PGA and polydioxanone, PDS, they have been widely utilized as the, as the

biodegradable polymers. They have been one of the very earlier ones, which have been established and later on, because of very stringent requirements, it becomes very tedious, to undergo the same process of getting an approval and then, using the new materials, or newly developed biomaterial, biopolymers as the biodegradable polymer, for the body, for the body implants, or for any drug, drug applications, or any, certain biodegradable applications in the body.

So, that is the overall deal with the polymers, that we can somehow, we have to engineer them and we have to undergo, undertake that design part, the testing part and the overall, overall aspect of work functionality, it will render, once it is inside the body. And, with that, I will end my lecture here. Thank you.