Introduction to Biomaterials

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Mechanism of Bioerosion

In this lecture, we learn about mechanisms of Bioerosion. As we have learnt that, polymers undergo biodegradation, Bioerosion, Bioabsorption and Bioresorption. In this particular lecture, we learn about, mostly about the Bioerosion, because, this is one of the very fundamental properties of a degradable polymer, that because, how we can utilize it, in terms of, as a drug delivery device, or maybe using some controlled degraded polymers for certain structural supplements, or by assisting drug delivery. So, there are certain mechanisms of Bioerosion that, that is what we will consider in this particular lecture. Also, we will learn about certain biopolymers. Because we have already learnt, learned about the biopolymers, how, what kind of polymers, which are available and how, how their chemical nature can really affect the degradation part. So, we will learn about the entry cases in this particular lecture, about how Bioerosion is responsible, in terms of degrading a particular biopolymer.

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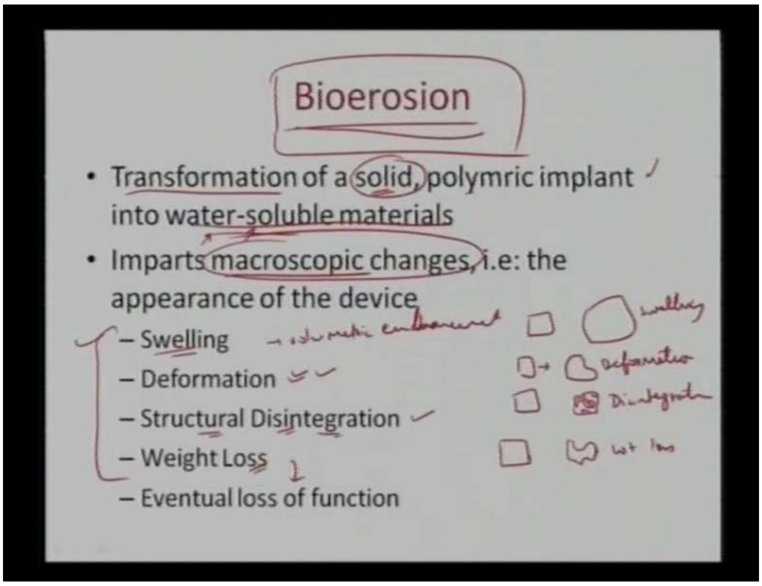

Bioerosion

- Transformation of a solid polymric implant into water-soluble materials
- Imparts macroscopic changes, i.e: the appearance of the device
  - Swelling
  - Deformation
  - Structural Disintegration
  - Weight Loss
  - Eventual loss of function

So, first of all, coming to the Bioerosion point, Bioerosion is nothing, but the transformation of a solid polymeric implant into certain water-soluble materials. So, we have a polymeric material, and it is water insoluble, and through certain activity, it basically becomes water soluble. So, this particular case, there are, certain macroscopic changes are occurring with the Bioerosion; and, those can be such as swelling, so, the overall appearance of the material itself is changing; so, that can occur by swelling; so, the overall volume of the polymeric material increases.

So, in this case, we have a volume, volumetric enhancement of a particular, volumetric enhancement can occur, or the material itself, itself can deform, because once this erosion is occurring, the overall deformation on the material will occur. So, in one case, we started with a smaller material, the swelling will be increase over its volume. So, this, in this case, it is swelling; but in case of deformation, the materials' shape can itself change. So, this is nothing, but the deformation. At the same time, there can be certain structural disintegration. If you had a (( )) polymeric starting material like this, then, later on, we can have certain structural disintegration; that overall structure maybe incorporated with certain porosities, out here and there. So, overall damage can occur through structural disintegration. There can also be weight loss, because once this polymer is (( )) into certain entity, it can be hydrolysis. So, the material will start losing its weight. So, initially, we started with certain material and then, later on, we will have somewhat different material; it might have lost its structural integrity as well, but at the same time, there is some weight loss.

So, we have swelling; we can have some deformation; we can have some disintegration and we can have weight loss. And eventually, all this, basically lead to eventual loss of the function, because, as this is, the functionality is dependent on the kind of material available, the quantity of the material be available, the weight of the material we have available, also, the chemical nature of the polymer, which is available at the end of a particular cycle of the storage. So, that is the reason, we can have certain, Bioerosion can be, it can basically, elicit, affect microscopically; the overall appearance can change either by swelling; so, the overall polymer can swell. It can deform; so, the deformation can also occur. There can be structural disintegration. So, the overall structure can also change and also, the weight can also be reduced, because of, because of its dissolution in the particular environment and that leads to eventual loss of function.

So, in this case, in case of Bioerosion, we see that, there is a transformation of a solid. So, the, the polymer has to be a solid; then only, it can basically get bio-eroded. So, it is a solid polymeric implant; it was initially water insoluble and that, after Bioerosion, it becomes fragmented into certain molecules, or certain set of polymeric chains, which become water soluble after the Bioerosion. And, that is imparting certain macroscopic changes. So, we can easily change the appearance, the change in the appearance of a particular device and that can occur with the Bioerosion; the material can either swell, or the device can swell. So, swelling is nothing, but the volumetric enhancement, in case, it will start observing the water. So, so, the hydrolysis might cause the increase in the overall volume. So, it will lead to the swelling; it can again, lead to deformation; because, once it is undergoing certain changes, some part might get deformed as well, depending on how the erosion is occurring. So, that deformation can also be a part of, that can also be a result of the Bioerosion. There can be structural disintegration, in terms of the dissolution of a particular polymeric polymer; it might start disintegrating. So, there can be weight loss also associated with the structural disintegration and that lead to eventual loss of the function.

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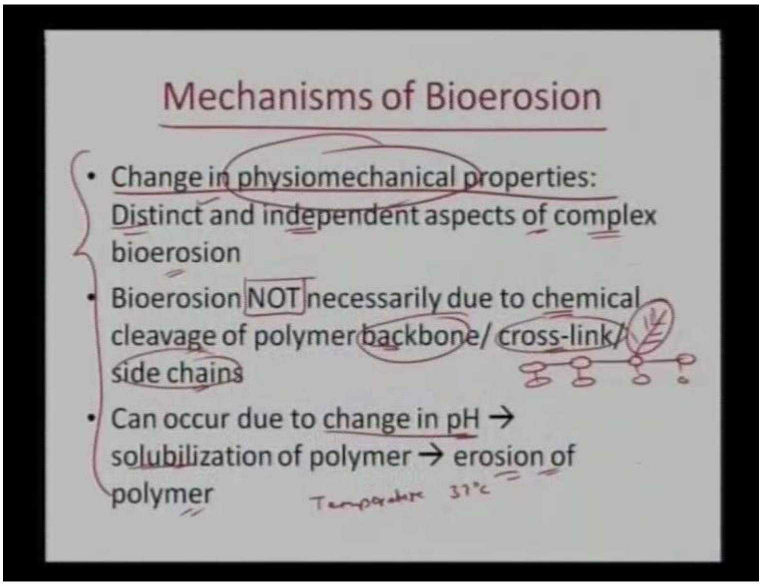

Mechanisms of Bioerosion

- Change in physiomechanical properties: Distinct and independent aspects of complex bioerosion
- Bioerosion NOT necessarily due to chemical cleavage of polymer backbone/ cross-link/ side chains
- Can occur due to change in pH → solubilization of polymer → erosion of polymer

Temperature 37°c

So, we can see that, the mechanism, though we talk about the Bioerosion, that it is changing the overall appearance, in terms of swelling, or by deformation, or by disintegration, or by weight loss. So, there are certain mechanisms, which are associated with the Bioerosion. And again, they results, they result change in the Physiomechanical properties. And again, all this mechanisms, they are distinct and they can even independent of each other, in terms of imparting this complex Bioerosion process, because it is a combination of certain entities, and as well as, they can be independent of this particular Bioerosion process. Again, this Bioerosion is always does not mean that, there is a cleavage of the polymer backbone, or the cross-linking, or the side chains. So, we were overall backbone, there can be disintegration of the overall backbone. This is the overall backbone. It can also be because of the cross-linking with other polymer, or it can also have some certain side chain. So, it have, it might have certain side chains, or the functional groups. So, that can also be (( )) during the Bioerosion process. So, again, it is always not limited to such things; it can, may not be always the backbone, or the cross-linking, or the side chain; it can also occur by certain change in the environment itself. So, if you have certain change in the environment, that can occur because of change in the pH. And, because of the change in the pH, we can also have certain solubilization of the polymer; and, that can lead to the erosion of the polymer. Additionally, we can also have certain other, other aspect; it can also be temperature. Because of the human body temperature is around 37 degree Centigrade, and depending on the overall, the T g, or the glass transition temperature of the polymer, there can be difference in its state. So, it can be either glassier, or it can become much more amorphous.

So, depending on that, it can again have very different mechanical properties. It can also have very different chemical properties. So, in terms, it will have a very different affinity for the, for the flow, or the intake, uptake of the water, and then, again, it can lead to very strong hydrolysis, once it is in the amorphous state. So, those feeble changes in the T g temperature as well, can lead to the Bioerosion. So, we can see that, mechanisms of Bioerosion, they are very very complicated; they can be very distinct and independent of each other; and, they lead to, they impart changes in the physiomechanical properties; and again, Bioerosion is not limited to the chemical entity, or the chemical cleavage, which can occur either in the backbone, or the cross-linking part, or the side chains to result the deterioration of the polymer. And again, the Bioerosion can also happen by changing the temperature, or by changing the p H, and that can again, alter the overall solubilization of the polymer. So, the overall solubility of the polymer can also get altered, in a particular environment and that can again lead to the erosion of the polymer. So, we can see the, how the complexity is, how complex is this particular process of Bioerosion, is there for the biodegradable polymers out here.

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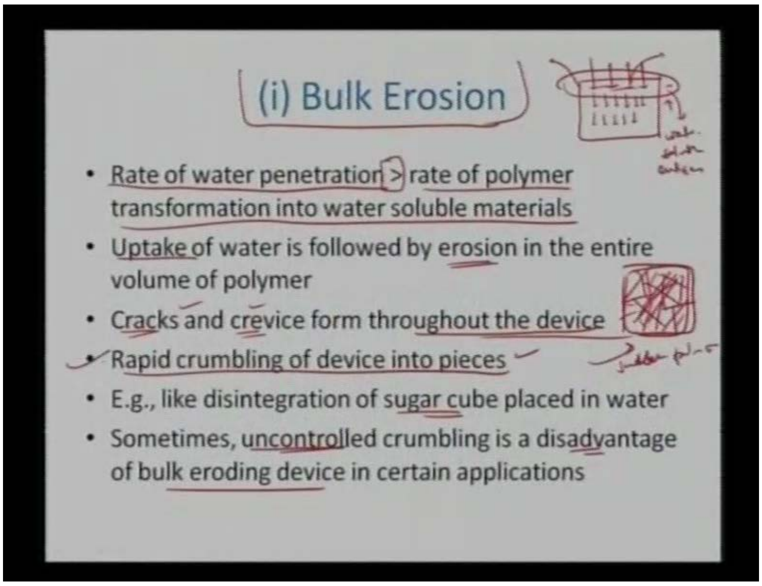

(i) Bulk Erosion

- Rate of water penetration > rate of polymer transformation into water soluble materials
- Uptake of water is followed by erosion in the entire volume of polymer
- Cracks and crevice form throughout the device
- Rapid crumbling of device into pieces
- E.g., like disintegration of sugar cube placed in water
- Sometimes, uncontrolled crumbling is a disadvantage of bulk eroding device in certain applications

So, again, depending on what kind of polymer it is, we can also have two kinds of erosion which can occur, one is the bulk erosion, or the second can be the surface erosion. So, first, let us consider the bulk erosion part. So, in this case, what is happening that, the rate of water penetration into the polymer is greater than the rate of polymer transformation into water soluble materials. So, we have a certain rate to a polymer, then, water is starts to seep in, and the rate of water penetration is much more faster; it will go much deeper into the polymeric material; by that time, that this entity, which is there on the surface gets solubilized in water itself. So, we have, rate of water penetrations; water is penetrated to a very rapid extent and in the mean time, there are some products which are forming along this region, which are getting disintegrated, or they are getting transformed to water soluble, water soluble entities, at a much slower rate. So, what is happening that, this process of dissolution of this particular polymer in to water soluble material, is happening at a much slower pace. So, water is seeping down to a very faster extent, even in the bulk of the polymeric material. So, in the process, what is happening is, that uptake of water is happening first, and that is being now followed by the erosion process. And now, that happens in the entire volume of the polymer; because our water penetration rate is much faster than the, than the rate at which the material will turn into water soluble component.

So, before it is really exposed to water, after the surface has been dissolved, the water is already penetrated into the bulk of the material, or the inner part of the material. So, what is happening in the process that, as soon as water is entering, it is getting already adsorbed, already absorbed, or the uptake has already happened; in the mean time, the surface is experiencing the conversion of polymer into water soluble components. So, what is happening, sooner, as soon as the water the material is turning into water soluble component, it leaves a certain pore, crevice, or a crack. So, now, that cracks and crevices, they start developing throughout the device; because of the process of water penetration is much faster, and the rate of dissolution of this polymeric material into water soluble component is much slower. So, with time, we will start seeing cracks and crevices in throughout the device, and that leads to the rapid crumbling of the device into pieces.

Because, as soon as we have a particular polymer, and we start seeing the cracks, and this process little slower than the water uptake, and we see rapid crumbling, because, water is now seeped throughout the material, to the bulk of the material, and that is what is leading to the overall sudden failure, or sudden crumbling of the device into the pieces.

So, it can be also seen, more like a dissolution of sugar cube. So, if we place a sugar cube in a water, it will start crumbling rapidly or suddenly. So, again, this crumbling is again uncontrolled; and, that becomes a disadvantage of the bulk eroding device, in certain applications; because we want the erosion to, to be complete in a certain controlled manner; and in this particular case, bulk erosion, the overall, overall deformation is occurring in an very uncontrolled manner. So, that is what we see that, in the bulk erosion, we have a water penetration, which is much more faster. So, it will rapidly occupy the overall bulk, or the inner part of the polymer. So, water is already seeped through out the polymer and in the mean time, the water soluble products will start forming and they will form randomly throughout any location. So, what is happening in the entire process that, now, we start seeing some cracks, crevices and pores, which are basically, now, being taken up by the surrounding liquid. So, in that particular case, once it is form certain cracks and crevices, very rapid crumbling of the device can occur. And, since this entire process is uncontrolled, that the process cannot be controlled; it is uncontrolled process; that becomes a disadvantage in certain cases. Because, certain, say for example, like in drug delivery, we would want very controlled degradation of the polymeric material. So, that, that can be now attained by, when we can control this bulk erosion, and we can make it much more surface sensitive. So, in case, when we have only surface erosion occurring, we can somehow get over this particular disadvantage. So, now, we come to the surface erosion.

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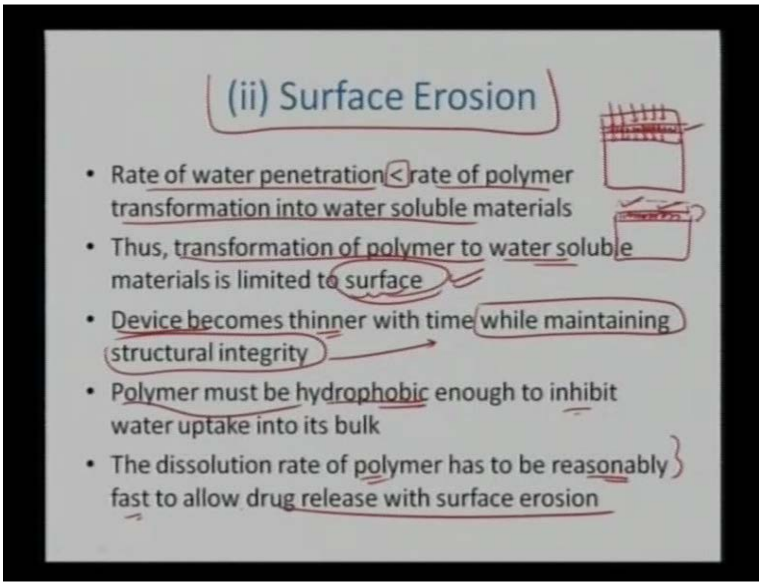

(ii) Surface Erosion

- Rate of water penetration < rate of polymer transformation into water soluble materials
- Thus, transformation of polymer to water soluble materials is limited to surface
- Device becomes thinner with time while maintaining structural integrity
- Polymer must be hydrophobic enough to inhibit water uptake into its bulk
- The dissolution rate of polymer has to be reasonably fast to allow drug release with surface erosion

So, in this case, what is happening in case of surface erosion, the rate of water penetration is much slower, in the rate of polymer which is not transforming into the water soluble materials. So, in this particular case, we have water penetration, it is occurring at a very slower rate. And, in the mean time, this is, this process is so slow, that by the time it goes incrementally, this surface now gets dissolved; then only, water can further penetrate to the second layer. And now, second rate start, second stage of the dissolution, basically occurs. So, it is more likes this. So, this thing is already been given, this state. So, once it has dissolved, then only, water can penetrate further and start attacking the surface. So, in this case, what is happening, we have rate of water penetration, which is occurring at a very slower, slower pace.

And, that is so slow, that the rate of, the rate at which the polymer is degrading, is much faster. So, the rate of degradation of polymer is much faster and then only, water is allowed to pass through it. So, what is happening in the process, as soon as the water is sitting on the polymeric surface, it sits, sits there for certain time and in the process, the polymers starts degrading. Only when the polymer has degraded, then only, the next layer of the polymer gets exposed to the water, which is sitting on the surface of the polymer. So, we can see very sharp interface. We can see very sharp interface between the polymer, which is, which had been degraded, and the polymer, which is now being exposed to the, to the hydrolytic environment. So, what is happening? So, the transformation of the polymer to the water soluble material, is now limited only to the surface; because the water penetration is so slow, that the water penetration, it cannot go to the bulk, and it can limit itself only to the surface. That is the advantage of this particular process, that surface erosion is now limited only to the surface, and it is specific to a particular material, depending on its hydrophobicity, or its chemical nature, or its molecular weight, and there are certain paradigm of parameters, or factors which will basically, dictate that.

So, what is happening in the process, the device starts becoming thinner and thinner, while maintaining its structural integrity. So, it is not like the previous case, when the entire polymer is now being, being uptaken by the water and there will be certain cracking and crevice formation in the entire of the material. In this case, only the surface starts degrading and the structure maintain its structural integrity; because it is only surface which is getting damaged first, or getting absorbed. So, it gets thinner and thinner because of the degradation process, of the surface degradation process, but it maintains its structural integrity. So, that is the advantage of this particular surface erosion.

So, again, in this particular case, the polymer must be hydrophobic enough to repel water, to inhibit water intake in to its bulk, or to let it go inside its inner part, the inner of the material. And again, the dissolution rate of the polymer has to be reasonably fast, to allow drug release with surface erosion. So, again, we need to control this particular dissolution; that has to be reasonably fast, though it is hydrophobic in nature, the dissolution rate has to be good enough, so that, we can allow enough drug to be released, within certain time duration. So, that is what is happening in this particular case. We are allowing surface, in the surface erosion, we have rate of water penetration which is much slower; so, in the process, only the surface is getting eroded first; after surface erosion, then only the next layer of the polymer gets exposed to water, and again, it starts becoming disintegrated into the water soluble components; and in the process, we can, the material maintains its structural integrity and for, for doing this particular kind of surface erosion, the polymer has to be much hydrophobic, to inhibit any water, water uptake into the bulk. At the same time, the dissolution rate of the polymer has to be controlled, or it has to be reasonably fast, so that, the drugs can be released in a timely fashion. So, that is the overall thing with the surface erosion; so, how it compares with the bulk erosion.

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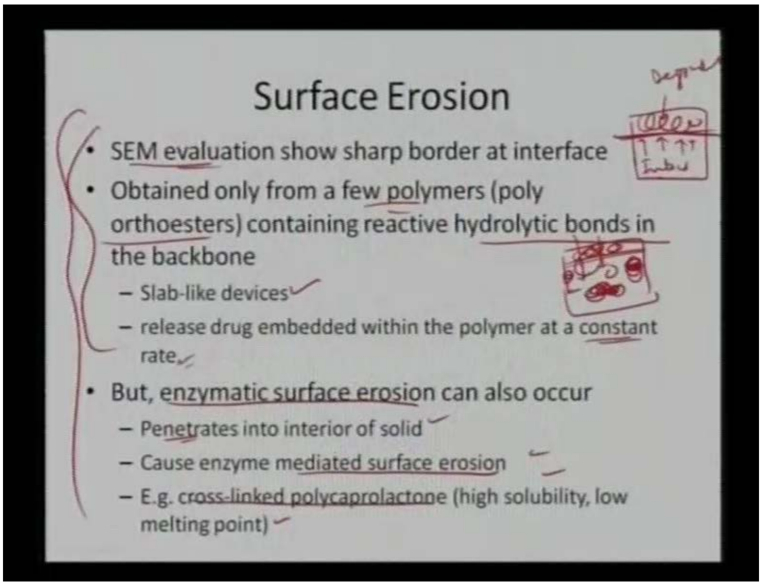

Surface Erosion

- SEM evaluation show sharp border at interface
- Obtained only from a few polymers (poly orthoesters) containing reactive hydrolytic bonds in the backbone
  - Slab-like devices
  - release drug embedded within the polymer at a constant rate
- But, enzymatic surface erosion can also occur
  - Penetrates into interior of solid
  - Cause enzyme mediated surface erosion
  - E.g. cross-linked polycaprolactone (high solubility, low melting point)

So, that is what is observed at the SEM evaluation. It shows very sharp border at the interface, because, once we have certain entity, like we have water soluble, and water insoluble; so, we can see very sharp interface, between the intact polymer and this is the degraded part. So, that is what we can see in the surface erosion; but in the bulk erosion, what we might expect is, the water has already seeped through. So, we might see certain areas; so, even though water uptake is on (( )) higher, like water uptake will be throughout, only certain material will be degraded here and there, locally.

So, that is, that is the actually problem with the bulk erosion; but in the surface erosion part, we see a very clear boundary, between the, at the interface. And again, it is obtained only from a few polymers, which are, such as polyorthoesters and which are containing certain reactive hydrolytic bonds in the backbone. And again, they can be utilized as slab-like devices, which can release drug, which is embedded, again in the polymer, at a very constant rate; because, in this case, only surface is getting degraded. So, depending on, we can easily estimate, or predict, what, what will be the degradation rate of the particular polymer. Apart from this, though we can say that, we are getting a very sharp interface, the, only the surface is getting degraded. So, we can somehow control and we can get a constant rate of dissolution, or degradation. So, it can have very controlled drug delivery, but that may not be the case all the time; because, there might be, certain enzymatic surface erosion can also occur. So, in presence of certain enzymes, they can also penetrate into interior of the, of the solid.

So, in case, when enzymes are getting penetrated, penetrated, they will tend to absorb some more water, and they can mediate the surface erosion, such as, such as, in case that, the cross-linked polycaprolactone, though it is high solubility and low melting point, this can occur, the enzymatic activity can occur in the cross-linked polycaprolactone. In this case, the enzyme can assist breaking of the cross-linking, or the, or the backbone, and in that particular case, it can allow, it can mediate the surface erosion of this particular polymer. So, that is what we can see that, the surface erosion, it is, it has very sharp interface and it can be shown only by a few polymers, so that, they can have a controlled rate of degradation; but again, though they might have very controlled drug delivery, they can also be assisted by certain enzymes, and in that particular case, it can penetrate much deeper into the material. And then, it can somehow lead to the surface erosion, which can happen to a, at much rapid rate, or it can also occur in the bulk of the material.

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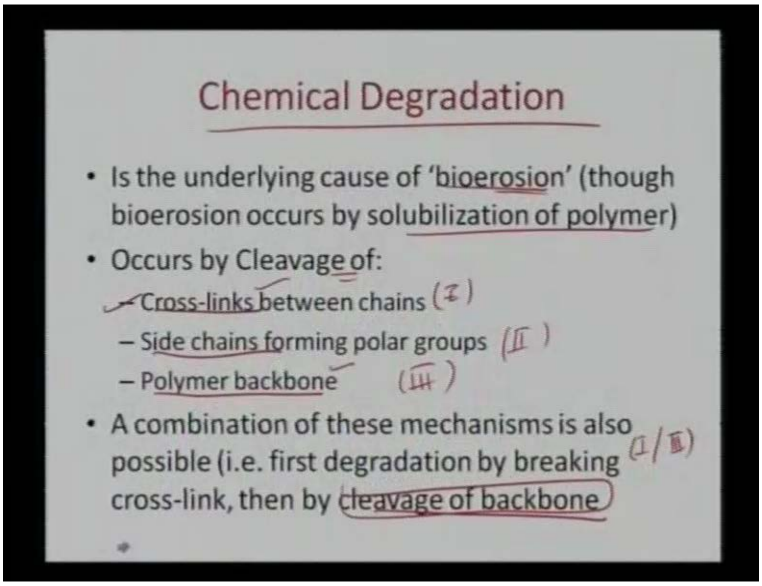

Chemical Degradation

- Is the underlying cause of 'bioerosion' (though bioerosion occurs by solubilization of polymer)
- Occurs by Cleavage of:
  - Cross-links between chains (I)
  - Side chains forming polar groups (II)
  - Polymer backbone (III)
- A combination of these mechanisms is also possible (i.e. first degradation by breaking cross-link, then by cleavage of backbone (I/III)

So, chemical degradation, it can, basically, it is the underlying cause of Bioerosion; though Bioerosion can occur, occurs by the solubilization of the polymer, the main reason behind the Bioerosion, is nothing, but the chemical degradation. And, chemical degradation is the occurrence of the cleavage. It can be either by the cleavage of cross-links, which, which is between the chains; it can also be the cleavage of the side chains, which form the polar groups, or it can also be the breakage of the polymer backbone itself. And again, there can be a combination of these mechanisms, which might be occurring. So, in this particular case, we can see, the combination of this mechanism can occur. First of all, there can be a breakage of the cross-links, and once it has formed a particular polymeric chain, then, it can lead to the cleavage of the backbone. So, in this case, we have mechanism one, cross-linking between the chains is getting cleaved; then, we have side chains, which are getting cleaved; and, in the third case, we have a polymer backbone.

So, in this case, we are seeing a combination of one and three. So, in this case, we are seeing a mechanism, first degradation of the cross-links, and then, formation of the, the degradation, the cleavage of the polymer backbone to cause the chemical degradation. So, there might be certain causes of the Bioerosion, but mainly, the Bioerosion is, the fundamental cause of the Bioerosion is basically, by the chemical degradation and that degradation can be either the removal of the cross-links, or it can again be the cleavage of the side chains, or it can be again the cleavage of the backbone structure of the polymer itself, so that, those are the basic reasons of the chemical degradation.

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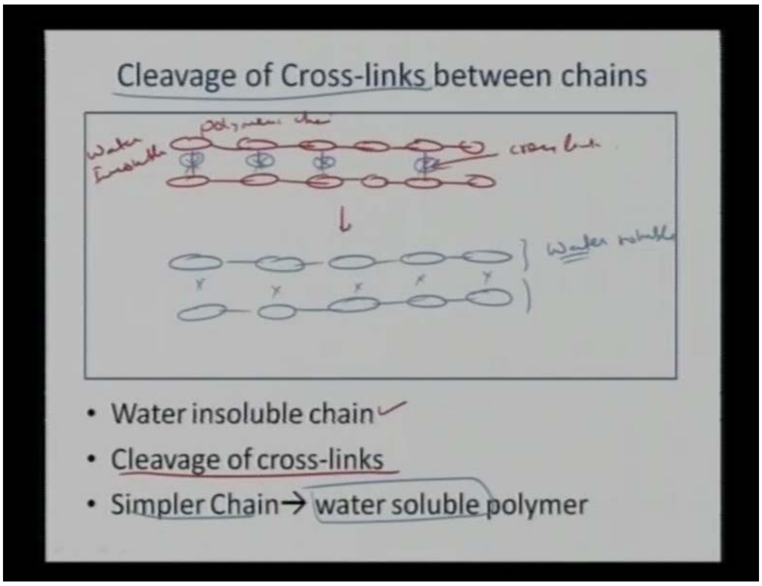

Cleavage of Cross-links between chains

- Water insoluble chain
- Cleavage of cross-links
- Simpler Chain→ water soluble polymer

And again, in first case, we can see the cleavage of the cross-link; it can also occur between the chains. So, once we can see that, we have a particular polymeric chain, and it might have certain cross-linking with the nearby chain. So, we can see, this is the main chain, and it is again, it has now certain cross-links. So, it can have certain cross-links out here.

So, we can see, there might, there might be certain cross-linking, cross-links out here and this is the overall chain, the polymeric chain. And, these cross-links are the basic responsible that, they, the overall polymer becomes very very water insoluble. So, in this case, we have water insoluble chain. And, in case one, in the mechanism, what is happening, we have, initially, we have water insoluble chain; and what happens is, the cleavage of the cross-links starts happening. So, in this, in this particular case, we have, we are left with…So, what is happening? We have, now, this similar polymer, polymeric chains, which are now standing in isolation, but without any cross-links. And now, the overall, the inherent nature of these chains are that, they become water soluble; because, there is no cross-linking available out here, between them; the chain gets much more freer; the cross-links, which is happening between, between the chains.

So, the overall polymeric chain, which are, which had a very strong cross-linking to the nearby chain, those links are now being broken; and now, that becomes a much more simpler chain; and, that simpler chain is much more, much more free and small, and that has nothing, but water soluble. So, that is what, that is what is happening in the, in this particular case, that we are, we are observing; that, the overall breaking of the cross-linking itself, to result a water soluble molecule. So, initially, we started with a water insoluble molecule, which had a very strong cross-linking and now, that breaks down to the very simple, water soluble polymeric chain.

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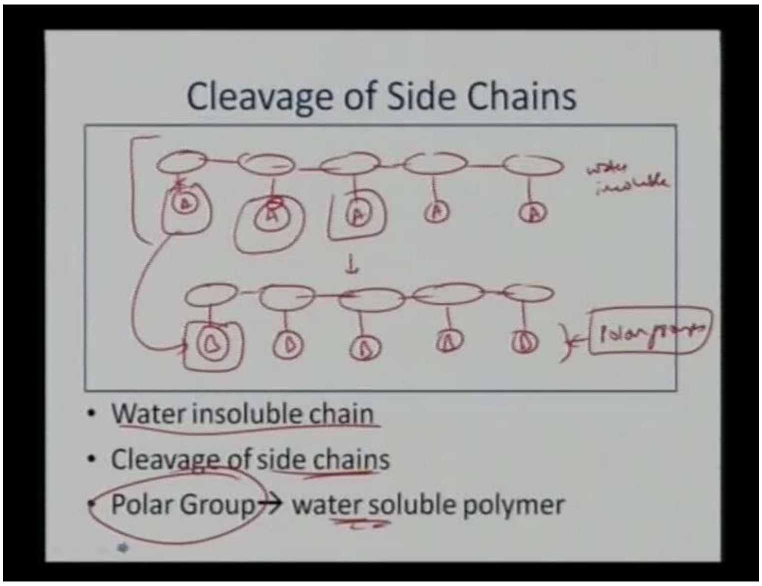

Cleavage of Side Chains

- Water insoluble chain
- Cleavage of side chains
- Polar Group → water soluble polymer

And similarly, what can happen in cleavage of the side chains. What is happening is that, we can have a overall chain with certain, with certain side chain; it can, it can have a certain side chain. And, due to non polarity of this particular polymer, this non polarity of this particular polymeric chain, this chain is water insoluble. But, in process, what is happening, the cleavage of all these polar chains of the side chains, can form something which is much more polar, or it can be much more charged. So, what is happening in the process, that the overall basic chain, the backbone of the chain remains as it is, but the side groups that now become charged. So, now, we have polar groups, which, which are attached out here, and that makes the chain water soluble. So, initially, we had water insoluble polymeric chain, and now, because of the cleavage of the side groups, or by some formation of, transformation of this side groups, or the side chains into charged polar chains; so, in this particular case, we have A transforming to B.

So, we, the overall, overall backbone remains the same, but the side groups, they, they basically, are cleaved, and they result a polarity, or the, or some sort of a charged region, or polar, which makes it water soluble. So, in this particular case, once we have a breaking of the, of the cross-linking; in this particular case, we have breaking of the, or the cleaving of the side chains, result water soluble polymer. So, we are, we are starting with water insoluble chain and we have cleaving of the side chains and that results formation of certain polarity, or the polar groups, and that makes the polymer soluble in water. But, there can be third mechanism as well; that, there can be the cleavage of the backbone itself.

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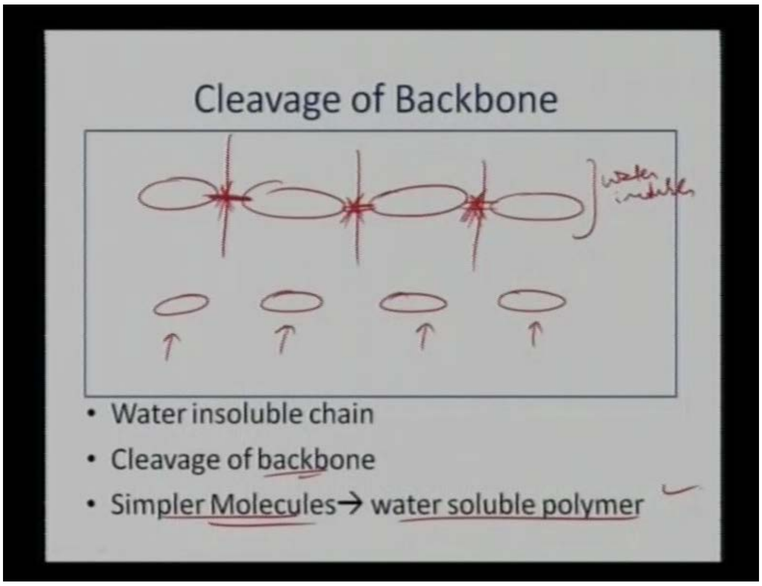

Cleavage of Backbone

- Water insoluble chain
- Cleavage of backbone
- Simpler Molecules→ water soluble polymer

So, in one case, when the overall chain itself is water insoluble, it can, it can lead to the, overall breaking of the backbone itself can also occur. The cleavage can occur along this particular bond, bond between the certain, certain smaller, smaller polymer, polymer molecules. So, in, in the process, what is happening, we might get certain isolated smaller soluble polymers. So, initially, we had water insoluble molecules, and the process, we are breaking the, or cleaving the bonding in the, with the backbone itself; the overall backbone itself, is now getting cleaved. So, we get small pockets of isolated polymers, which are very small, which are very simpler molecules. So, that is what is happening in this particular case to make it water soluble. So, in first case, we have a breakage of the cross-link itself; in second case, we have cleaving of the side chain and third case, the cleaning of backbone is occurring. And, this might be the entire, or it might be the final, basically, the final process, which might be occurring in the chemical degradation, as soon as polymer is getting totally, becoming totally water soluble, or getting totally cleaved. So, that is what, this might be the eventual process, which, which is basically dominating, in terms of dissolving, or Bioeroding, eroding a biodegradable polymers; so, that is what we can see out here.

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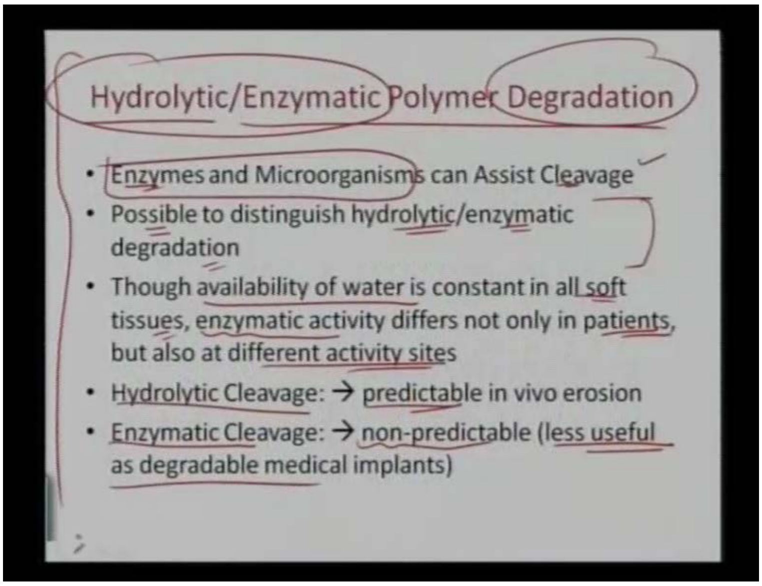

Hydrolytic/Enzymatic Polymer Degradation

- Enzymes and Microorganisms can Assist Cleavage
- Possible to distinguish hydrolytic/enzymatic degradation
- Though availability of water is constant in all soft tissues, enzymatic activity differs not only in patients, but also at different activity sites
- Hydrolytic Cleavage: → predictable in vivo erosion
- Enzymatic Cleavage: → non-predictable (less useful as degradable medical implants)

And, in certain cases, the hydrolytic, or enzymatic polymer degradation. In case, we have hydrolytic, or enzymes can also, sometimes, assist cleavage; apart from only the water, or the hydrolytic environment, sometimes enzymes and microorganisms can also be, they can also serve as an agent, to cleave the particular bonding between the polymeric chain; it can also cleave, either the, either the cross-links, or the side group chain, or also, the backbone itself.

And again, but again, in this both the cases, it becomes possible to distinguish the hydrolytic, or the enzymatic degradation; because, in one case, we know that the, in one case, we have hydrolytic degradation; it can occur only on the surface; whereas, enzymatic degradation can occur, even in the bulk of the material. And that is possible, why because, availability of water is constant in all the soft tissues; but, the enzymatic activity, it differs very much; not only in patients, but also at the different activity sites. So, depending on where we have more enzymes, it can show a very drastically different, very drastically different behavior. Because, if you have certain water, in certain localized patients, or cells, the overall availablity of water is constant, in all the soft tissues.

So, the soft tissue, water content is almost constant, whether it is, it differs very slightly either in patients, or at different locations of the particular patient. But enzymes, their overall concentration is very, very different, not only in patients, but also at the different sites, where they are present. So, again, hydrolytic cleavage, it becomes much more predictable; because now, we know that, the overall concentration of water in cells, or in patients, is almost constant. So, the degradation will occur in a very controlled or predictable manner. Whereas, once we have enzymatic cleavage, it becomes very, very unpredictable. So, in this case, we have very, it becomes very less useful material, as the degradable medical implant. So, again, we can see, the degradation can occur either via hydrolytic, or enzymatic conditions. So, this hydrolytic degradation is very, very predictable, because the water content is very, very similar, either in cells, or at different, or even in patients, whereas, the enzymatic activity differs very, very drastically, either in cells, or in different patients. So, that assist us, in basically, delineating how the degradation is occurring; whether it is, whether it is a occurring either by hydrolytic, or by enzymatic action. So, if the material is deforming very, very in a predictable manner, it is because of the hydrolytic degradation; whereas, if it is unpredictable, it is because of the enzymatic activity.

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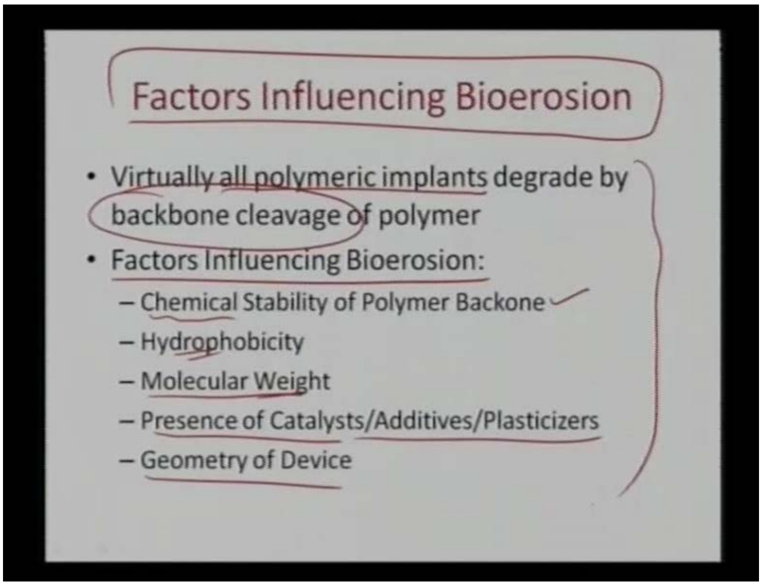

Factors Influencing Bioerosion

- Virtually all polymeric implants degrade by backbone cleavage of polymer
- Factors Influencing Bioerosion:
  - Chemical Stability of Polymer Backone
  - Hydrophobicity
  - Molecular Weight
  - Presence of Catalysts/Additives/Plasticizers
  - Geometry of Device

So, that part again, we can clarify; we can see, or we can easily emphasize, through, through again, factors, which dominate the, which influence the Bioerosion. Basically, or virtually, all polymeric implants which degrade, they degrade by the backbone cleavage. So, as I said earlier that, the backbone cleavages are eventual consequence of all the processes; because, that is what is resulting in the overall degradation of a particular polymer into water soluble components. Again that, there are, but apart from that, there are certain factors, which can influence the Bioerosion and those can be, chemical stability of the polymer backbone itself. So, the polymer backbone itself is much more stable, it will not allow the, (( )), degradation of the polymer. It can also be, it can be also affected by the hydrophobicity; if the, if the material is hydrophobic in nature, it will not allow much water, water uptake.

It can also be dependent on the molecular weight. So, depending on the, if the material has a high molecular weight, it has much more cross-linking, then, obviously, the overall degradation will be much more slower. Again, the presence of catalyst, additives and plasticizers. So, depending on the assistance, which it can get from either catalyst, additives, or plasticizers it can affect, or it can be, the overall Bioerosion rate can be controlled. And again, the geometry of device; depending on how the device has been fabricated, or processed, we can have very strong influence of how the, how the particular Bioerosion will occur in a particular device. So, we can see that, all the polymeric materials which are now being degraded by the backbone cleavage. And, they can, they can be affected by the chemical stability of the polymer backbone itself, by the hydrophobicity, even by the molecular weight, or by the presence of external additives, catalysts, agents, plasticizers, or even the geometry of the device. Let us look them one by one, so, we can get a better, better feel of it.

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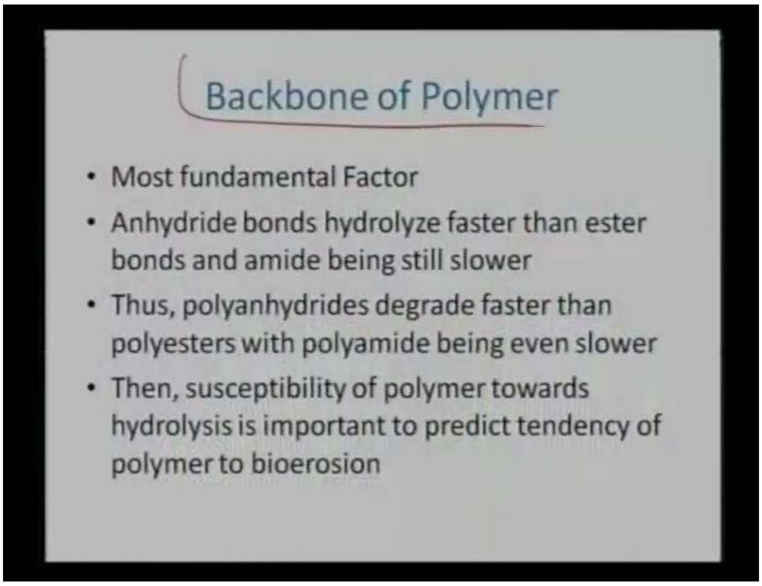

Backbone of Polymer

- Most fundamental Factor
- Anhydride bonds hydrolyze faster than ester bonds and amide being still slower
- Thus, polyanhydrides degrade faster than polyesters with polyamide being even slower
- Then, susceptibility of polymer towards hydrolysis is important to predict tendency of polymer to bioerosion

So, the backbone of polymers, in terms of deciding the biodegradability, or the overall disintegration of the particular polymer. It is one of the most fundamental factors. And, in certain cases, it has been dictated by the chemical nature of the polymer. In some, in some, like in cases, the anhydride bonds, it will hydrolyze much faster. So, hydrolization rate of anhydrides, it is much faster than the ester. And again, ester; ester's degradation rate is much faster than that of an amide. So, we can see that, anhydride, anhydride bonds, they hydrolyze very, very rapidly. So, that is what we are seeing, and thus, they will degrade at a much faster rate. So, polyanhydrides will degrade much faster in comparison to the esters, or polyesters, and polyamide might, might be much more stabler, or they will degrade at a much slower rate than that of an ester. So, so, we can have a polyanhydride, which can degrade in very short, short duration, followed by a polyesters, which can degrade at much slower rate, and polyamide, even being slower than the polyesters.

So, again, the susceptibility of the polymer towards the hydrolysis, is also very important. Though, this is dependent on the overall chemical nature, like anhydride, ester and the amide bond, there is additional factor of the hydrolysis part. How, how much they are susceptible to the uptake of water, and then, in combination with that, we will have some hydrolytic degradation, and that will be helpful, in treating the overall tendency of polymer to degrade, or get Bioeroded. First of all, we have the chemical nature and then, that has to be assisted by the overall hydrolysis part of it. How, how the hydrolysis, hydrolysis is occurring? What is the overall susceptibility of this particular chemical, in terms of, in terms of uptake of water, and then, eventually leading to the degradation of the biopolymer.

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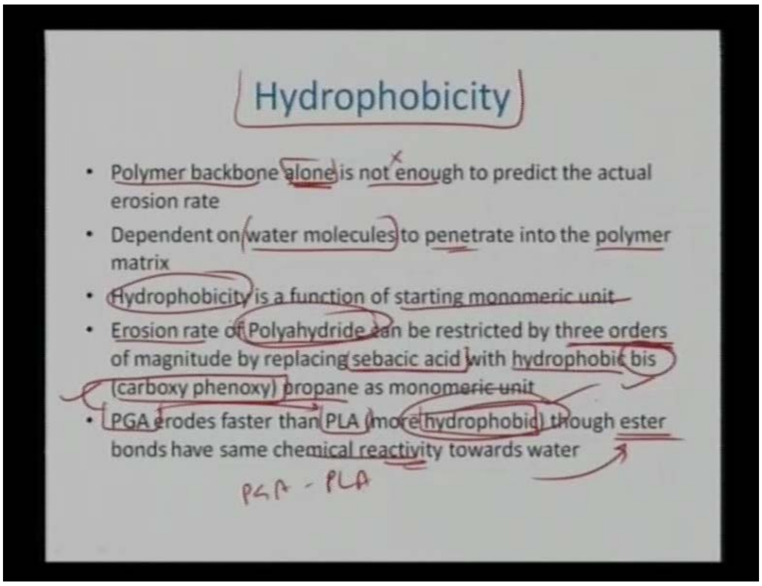

Hydrophobicity

- Polymer backbone alone is not enough to predict the actual erosion rate
- Dependent on water molecules to penetrate into the polymer matrix
- Hydrophobicity is a function of starting monomeric unit
- Erosion rate of Polyahydride can be restricted by three orders of magnitude by replacing sebacic acid with hydrophobic bis (carboxy phenoxy) propane as monomeric unit
- PGA erodes faster than PLA (more hydrophobic) though ester bonds have same chemical reactivity towards water

PGA - PLA

So, again, as we see that, the polymer backbone alone, is not enough. We also need some other parameters, which is nothing, but the hydrophobicity. So, depending on how much is the overall affinity of a particular chemical to take water, to uptake water and penetrate into (audio break) the polymer. So, again, then, the hydrophobicity becomes a function of the starting monomeric unit; because, the chemical nature of the material, it is the, it start off with the monomeric material. So, monomeric material decides, what is the overall affinity of this particular chemical, towards a hydrophobicity. So, we can see that, there is a combination of chemical, as well as the hydrophobicity, in terms of dictating the bioerosion. And again, in this case, we can see the erosion rate of polyanhydride, it can be restricted by three orders of magnitude. As soon as we replace the sebacic acid, with the hydrophobic bis carboxy phenoxy propane.

So, in one case, once we have this polyanhydride, if we can replace this, which can be, if we can replace this sebacic acid, with much more hydrophobic monomeric unit, which is hydrophobic bis carboxy phenoxy propane, and then, that one actually is becoming, making it super hydrophobic; it is making it much more hydrophobic; it can, it can increase the super hydrophobicity by around 1000 times, or, so, three orders of magnitude. So, that is what is happening; that is what is effect of hydrophobicity. And again, we can see that, the PGA can erode much faster than PLA; because, PLA is much more hydrophobic in nature; though, in the both the cases, we have the same ester bonds. So, in both PGA, as well as PLA, we have same ester bonds, but though, they have, around the same chemical reactivity, but because of hydrophobicity, PGA is dissolving at much faster rate. So, in this particular case, we can see the overall effect of hydrophobicity that, though the polymeric backbone is one of the very key, key, key things about the polyamides, polyesters and polyanhydrides, the polyanhydrides being the fastest, but faster degrading material, but again, apart from that, the overall susceptibility of water uptake to penetrate into the polymer and then, lead to hydrolysis, is very, very different. So, like in certain cases, if the overall erosion rate can be restricted by around 1000 times, or the three orders of magnitude, just by replacing sebacic acid with much more super hydrophobic, which, with much more hydrophobic bis carboxy phenoxy propane in the polyanhydride, it can reduce its degradation rate. And again, PGA and PLA, they have the same chemical reactivity, but because of hydrophobicity of PLA is much higher, then, it can degrade at much slower rate than, comparison to that, compared to that of PGA. So, that, that is the overall deal with the hydrophobicity.

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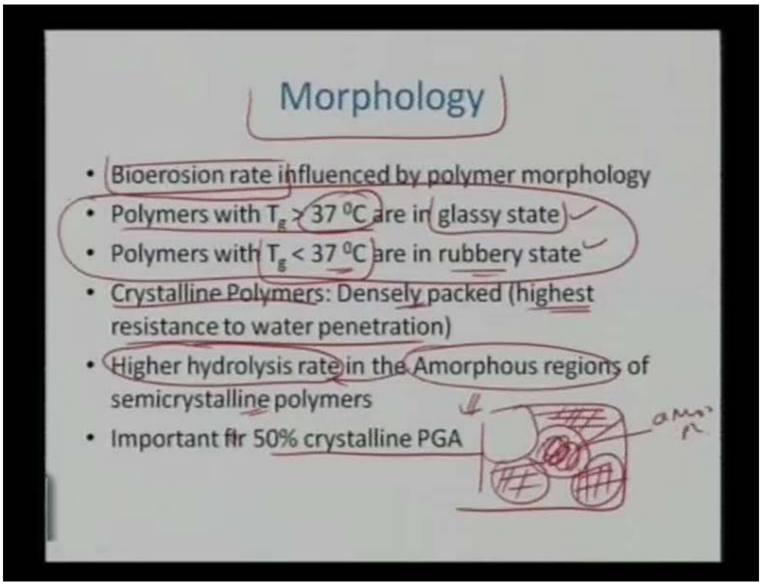

Morphology

- Bioerosion rate influenced by polymer morphology
- Polymers with $T_g > 37\,^0C$ are in glassy state
- Polymers with $T_g < 37\,^0C$ are in rubbery state
- Crystalline Polymers: Densely packed (highest resistance to water penetration)
- Higher hydrolysis rate in the Amorphous regions of semicrystalline polymers
- Important flr 50% crystalline PGA

So, apart from the overall, overall backbone structure, or the chemical nature of the material, apart from its hydrophobicity, morphology is also very, very critical, in terms of dictating the bioerosion, with bioerosion rate, which is now occurring in the degradable biopolymers. Like, in certain cases, when the polymers have a T g much greater than 37 degree centigrade, they are in the glassy state; and, this 37 degree centigrade is important because, that is the human body temperature. So, polymers with T g lesser than 37 degrees centigrade, they will be more in a rubbery state. So, so, in this case, what is happening, when T g is very, very, when T g is greater than 37 degree centigrade, and so, below this temperature, material will be very, very hard, or it will be in glassy state. And, once they have a T g of less than 37 degree centigrade, so, heating above this particular temperature, the, the polymer will become very, very soft. So, it will be become more like a rubbery state. So, in certain cases, the polymers can be the amorphous, crystalline or semi-crystalline.

So, in the case of crystalline polymers, polymers are very densely packed. So, once the densely, densely packed, that, that is very, that is, it becomes highly improbable that, water can get very easily into the bulk of the material. So, once the, for the crystalline polymers, they show highest resistance to the water penetration.

So, there is the combination of all this. So, first, let us see only the crystalline polymers, that they are densely packed. So, they show very high resistance in water penetration. And again, so, the, so, again, in semi-crystalline what happens is, there is higher hydrolysis rate, only in the localized region, where we see amorphous regions. So, amorphous regions of the semi-crystalline polymer, they show very high hydrolysis rate. And again, this particular part becomes very important, because, this beccomes very important for 50 percent crystalline PGA; because, in this particular PGA, we will have certain regions which are amorphous, and certain regions which are crystalline. So, we have certain regions, which are very highly crystalline and certain regions which are highly amorphous. So, the, the amorphous regions will now be getting targeted first. So, this amorphous region, this one will start degrading first. So, the overall bioerosion rate is also dependent on the overall morphology; if the polymer is much more crystalline in nature, it, it will resist the water penetration; if the material is semi-crystalline, obviously, the polymeric, the, the, if semi-crystalline, then, obviously, the amorphous region will get targeted first and the crystalline nature, the crystalline region will remain intact, to a very larger extent, in comparison to the amorphous material.

So, so, those polymers which are semi-crystalline, such as PGA, 50 percent crystalline PGA, that will experience some degradation, mostly in the amorphous regime, and that will tend to crumble the overall structural integrity of the PGA itself. So, that is what is very, very critical. And again, the polymers, they have different glass transition temperature. So, depending on that also, the material can either be, remain glassy, or become rubbery. So, again, glassy materials will have higher resistance in water penetration, whereas, rubbery materials, they tend to degrade much faster.

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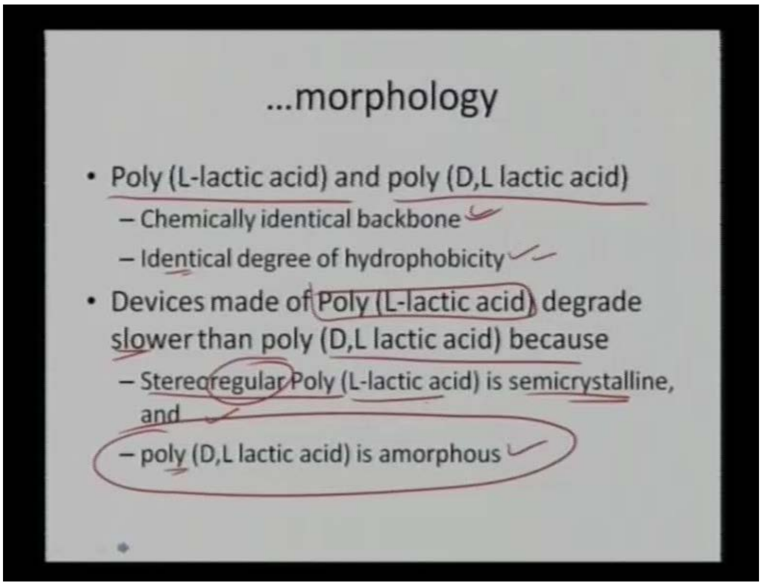

...morphology

- Poly (L-lactic acid) and poly (D,L lactic acid)
  - Chemically identical backbone
  - Identical degree of hydrophobicity
- Devices made of Poly (L-lactic acid) degrade slower than poly (D,L lactic acid) because
  - Stereoregular Poly (L-lactic acid) is semicrystalline, and
  - poly (D,L lactic acid) is amorphous

So, again, like in case, the morphology is very, very critical, because in case of, say poly L-lactic and poly D, L lactic acid, they have identical backbone. So, the, the overall backbone is very, very similar; they have identical degree of hydrophobicity as well. So, so, obviously, we will tend to expect, oh, they should degrade at, at the same rate, because the poly L-lactic acid, poly D, L lactic acid; similar chemical nature; similar hydrophobicity; but because of the difference in crystallinity, like our stereo-regular poly L-lactic acid, it is semi-crystalline in nature; whereas, is poly D, L lactic acid is amorphous.

So, in this case, we can see stereo-regular poly L lactic acid, it becomes much more semi-crystalline and it has, since it has much more regimes of crystalline, crystalline, it has much more crystalline regimes, it is, it basically degrades, at much slower rate. So, devices made of poly L-lactic acid, they will degrade at much slower rate than that of a poly D, L lactic acid, because, or poly D L lactic acid is amorphous in nature. So, we can see in this particular example that, though have chemical, they have similar, or identical chemical backbone, they have identical, identical degree of hydrophobicity, but because of the difference in the morphology, or the overall structure, that one is amorphous, one is crystalline, semi-crystalline, that is leading to the change in the overall degradation of the material. So, that is, that become, that, that is very, very critical part of it as well. So, we are concerned about the overall backbone, the overall hydrophobicity, as well about the morphology of a particular polymer, in terms of dictating the degradation rate.

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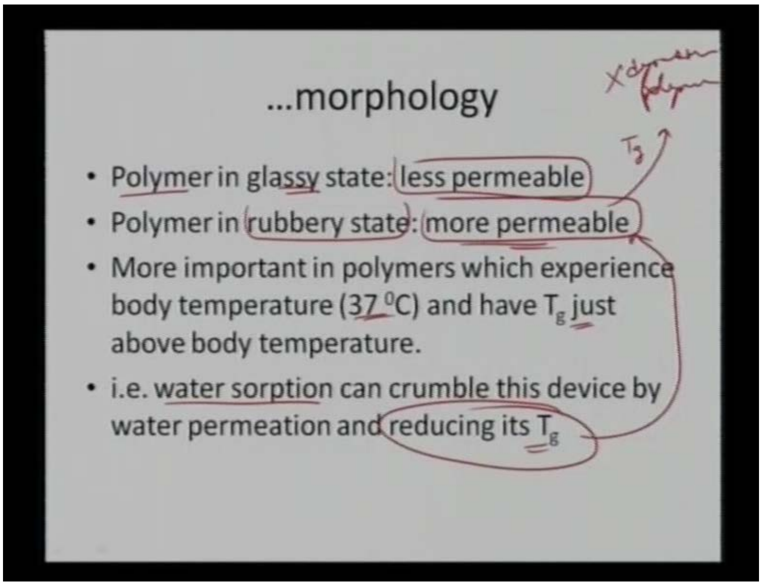

...morphology

- Polymer in glassy state: less permeable
- Polymer in rubbery state: more permeable
- More important in polymers which experience body temperature (37 ^{0}C) and have T_g just above body temperature.
- i.e. water sorption can crumble this device by water permeation and reducing its T_g

Again, as we talked about the glassy and rubbery state, that is dependent on the glass transition temperature. So, as we said earlier, the polymer which is in the glassy state, it is less permeable; whereas, polymer in the rubbery state is much more permeable. So, obviously, when the permeability is very, very high, water can seep in at much faster rate. So, so, the particular polymers, which have, which actually experience body temperature and they have T g just above, or just below the body temperature, they will be much more rubbery in nature and in case, there are certain fluctuations in temperature, or the water can basically seep through, or there are certain enzymatic activities, that can lower the T g to below 37 degree centigrade; even when the T g is above 37 degree centigrade, marginally above 37 degree centigrade, enzymatic actions, or hydrolytic actions, can reduce this T g to, say, below 37 degree centigrade and that will tend to crumble the device. So, because water sorption can occur, or enzymatic action can occur and that can reduce the glass transition temperature of the polymer and that will make it rubbery; and rubbery means, more permeable, and that will lead to a strong degradation of the absorption of the polymer.

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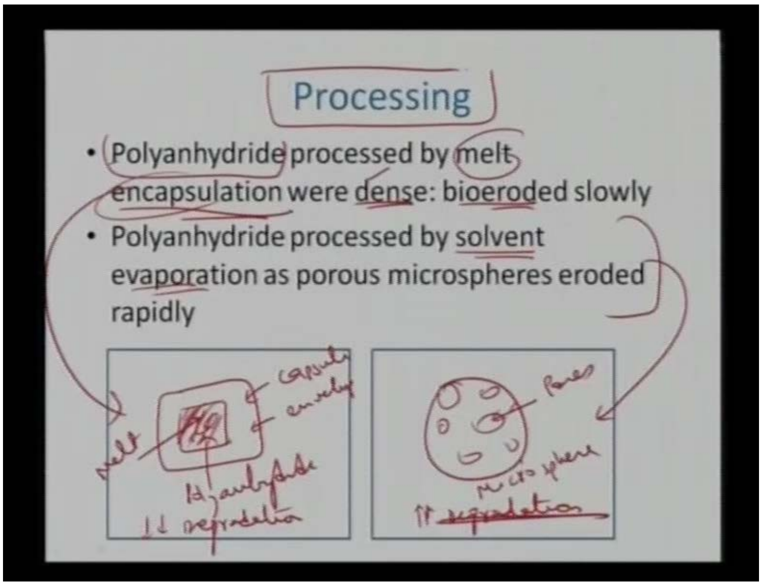

Processing

- Polyanhydride processed by melt encapsulation were dense: bioeroded slowly
- Polyanhydride processed by solvent evaporation as porous microspheres eroded rapidly

So, that is what is happening that, low, if the temperature is above the T g, the material will become very, very flexible and much more permeable and that will lead to the overall rapid degradation of the polymer out there. And, apart from that, this enzymatic, enzymatic action, or the overall nature of the morphology, processing is also very, very critical; because, processing level, is the one which can dictate, or change the overall structure, or the morphology of the processed polymer. So, in certain case, like when we have polyanhydride, which is now being processed by melt encapsulation, it was very, very dense. So, it is eroding very, very slowly. So, we have certain melt encapsulations. So, we have, we have certain melt; it has now been encapsulated. So, we are now getting certain device, polymeric polyanhydride. So, this is, this is the capsule; this is the envelope and this is the overall melt.

So, now, once we have polyanhydride, which has been process by melt encapsulation, so, we have a, kind of a capsule over it, so, that makes it very very dense. So, we have a dense structure, and same polyanhydride, which is now made by solvent evaporation, it will, it will result in a, kind of a microsphere. But now, this microsphere has many, many pores, internal pores out there. So, we have pores; this is a, kind of a microsphere. So, now, this one will degrade at much rapid rate. So, very rapid degradation of this microsphere, which has been prepared by solvent evaporation; whereas, for this one, the degradation rate is very, very slower, because, this is very dense. So, we have polyanhydride, which is processed by the melt encapsulation; it is much more, it is much more resistant to degradation; whereas, the solvent evaporation, there is much more prone to degradation, because it has very, very large number of pores, and it is very, very loosely packed, or very less dense material. So, that, that part, we can attain from the different processing around. So, the altering the processing around, we can again change the overall degradation of a particular material.

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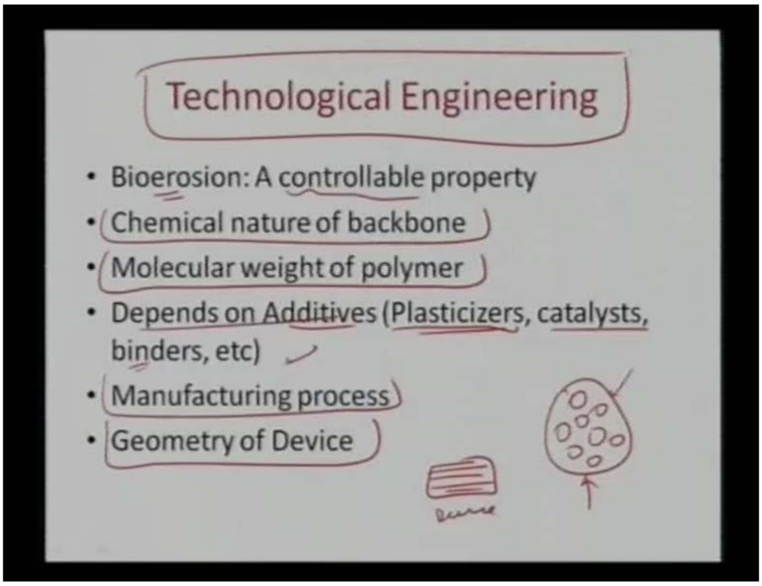

Technological Engineering

- Bioerosion: A controllable property
- Chemical nature of backbone
- Molecular weight of polymer
- Depends on Additives (Plasticizers, catalysts, binders, etc)
- Manufacturing process
- Geometry of Device

So, the overall technological engineering, we can say that, the Bioerosion is not an inherent property; it is a controllable property. So, that part, we can very, understand right now, from this particular lecture, the Bioerosion can be easily controlled depending on the overall backbone, the kind of enzymatic actions which can, which can be plausible, or again, when they have the overall hydrophobicity of the material; and even when we have particular hydrophobicity, if we can alter the structure of the, morphology of it, or by which we can really process the material, so, it becomes a very controllable property. So, we can somehow make it dependent. It is dependent on the overall chemical nature of the backbones; if we can alter the backbone, we can again control the Bioerosion by changing the molecular weight of the polymer'; we can again have much, much control on the Bioerosion; it also depends on the additives.

So, kind of additives we are adding, it can, plasticizers, catalysts, binders, so, those can also alter the overall degradation of the polymer. Again, it is dependent on the manufacturing device. Again, a geometry of device can also play a important role in terms of its degradation; like, if you have certain device, which, which is, which is kind of a spherical in nature, so, it has a very high surface area, and if we, if we can introduce certain pores in, pores in it, so, this device might degrade at a much faster rate, than a kind of a slab, which is highly dense. So, this dense, dense, particular dense, a device may degrade at much slower rate in comparison to a, in comparison to a porous spherical entity. So, there are certain technological engineering is also possible, by controlling the overall chemical, chemical nature of the backbone, by controlling the molecular weight, or by controlling the additives, or even by the manufacturing process. So, those are certain parameters which are available to us, in terms of dictating the degradation rate, which we want in a degradable polymer.

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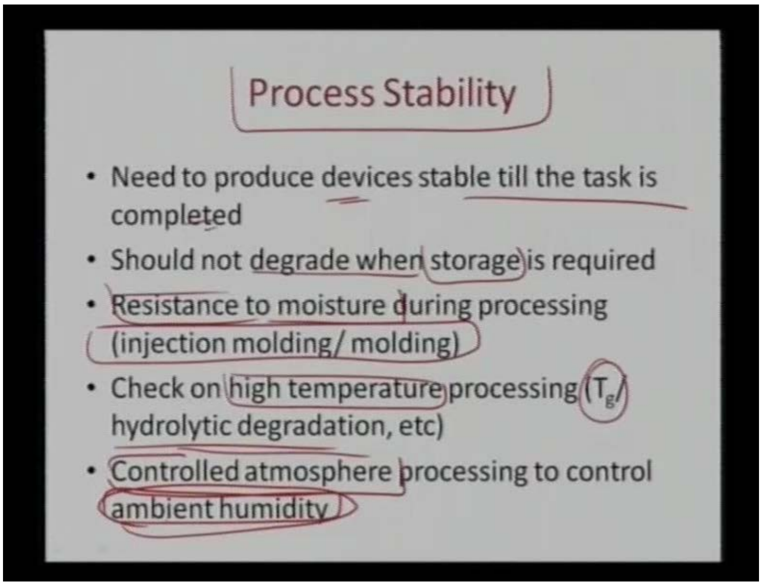

Process Stability

- Need to produce devices stable till the task is completed
- Should not degrade when storage is required
- Resistance to moisture during processing (injection molding/ molding)
- Check on high temperature processing (T_g/ hydrolytic degradation, etc)
- Controlled atmosphere processing to control ambient humidity

But again, we have certain limitations; like, we want the, there is something called process stability; that, we need the device to be stable enough, for a much longer time, till it has completed its task. So, the device starts degrading at much faster rate than predicted, then, it has not served, served its purpose. So, in case, we want to inject a particular drug into the material, into the body, say for a duration of 1 year, and in the process, the, the overall device is getting consumed in, say, 4 months. So, what about the remaining 8 months? So, it has not completed its task for the next 8 months and then, that next 8 months can be highly critical and that might lead to, damage the overall functionality of the, of the person, or the, or the patient itself.

So, in that particular case, we need to produce devices that are stable till the task is, basically completed. So, they should not degrade, when they are supposed to store the particular drug. So, again, they should be resistant to moisture, when they are being processed; because, during processing, it should not start degrading there itself, when the processing, processing is occurring; because, processing is occurring at much high temperatures, so, like an injection molding, or compression molding; so, they should be resistant to moisture, because, if there is some moisture, moisture uptake, they can start degradation. So, they need to be controlled; they should be processed in controlled atmosphere, or they should be resistant to moisture during the processing. So, we should keep a check, either on the temperature, as well; as well as the transition, glass transition temperature, or the hydrolytic degradation, when the processing is occurring. And, we should do the processing in a controlled atmosphere. It should be controlled, the ambient humidity as well. So, in this particular case, we have a controlled atmosphere, keep a check on temperature, as well as the overall humidity of the chamber, so that, the device, it should not start degrading, when the processing is occurring. So, we need to keep the device much stabler, for much prolonged time, so that, it can complete its task, what is assigned to it.

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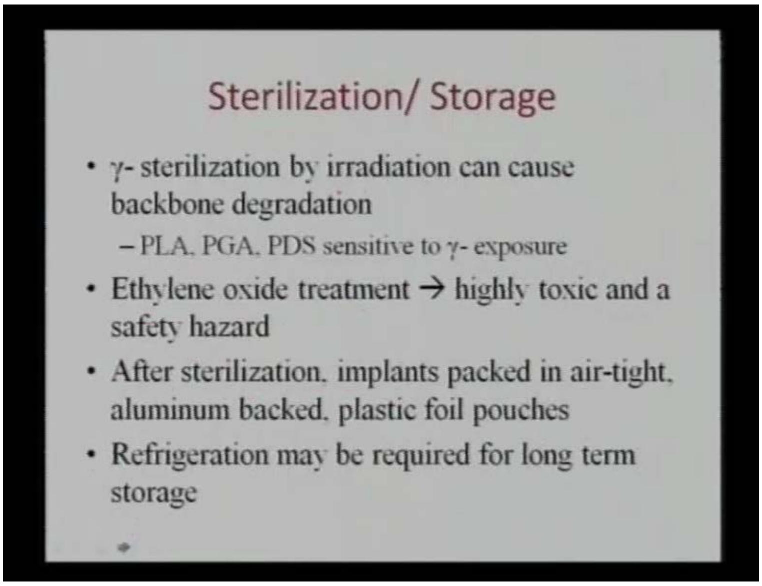

Sterilization/ Storage

- γ- sterilization by irradiation can cause backbone degradation
  - PLA, PGA, PDS sensitive to γ- exposure
- Ethylene oxide treatment → highly toxic and a safety hazard
- After sterilization, implants packed in air-tight, aluminum backed, plastic foil pouches
- Refrigeration may be required for long term storage

And apart from that, the materials also need to be sterilized. And also, they need to be stored for certain duration, before they are injected into, into the patient. So, there can be sterilization by gammas, gamma irradiation; but, this gamma irradiation can cause backbone degradation, such as, some polymer, such as PLA, PGA, PDS, they are highly sensitive to gamma exposure, and that leads, leads to damage of its backbone. So, in this case, this, this sterilization may not be really good enough, but gamma sterilization can also be useful for certain other polymers. So, in case of PLA, PGA and PDS, ethylene oxide treatment can also be given; but, the problem with ethylene oxide is that, it is highly toxic and it is basically, a safety hazard. So, that is again, gives and takes of certain materials, that if they are prone to gamma damage, then, they have to be treated with ethylene oxide; but again, ethylene oxide, we need certain concerns about its safety; that it needs to be properly cleaned up, because it is highly toxic and it can also become a safety hazard.

And again, after it has been sterilized, the material has to be kept in an air tight container, which is aluminum backed and it is again in, kept in the plastic foil pouches, so as to avoid the degradation part of it. And, in certain case, cases, even refrigeration may also be necessary. So, for long term storage, because, if we want to use a device after a certain, prolong, after a certain whole period, the material, the overall device needs to be, to be kept under refrigeration, so that, it should not degrade with time. So, we can see, there are certain aspects, which are related to either processing, or the sterilization part. So, that is how, we can somehow, that is how, we can control the overall degradation and be able to process it successfully, sterilize it, as well as store it, for certain time, so that, it can be used successfully in patients.

So, that is what we saw in this particular lecture, that we have polymeric degradable polymers, for which we can, for which the erosion, or the bioerosion can be controlled, by, which is basically being governed, by the overall chemical affinity, or the backbone structure. It is also governed by the hydrophobicity of the material; it is again, it is again governed by, though they have the similar hydrophobicity and the similar backbone, they are, they are governed by the overall morphology of it, which is again the crystallinity, or the amorphous nature. And again, the processing can also induce some sort of a dependence of how the material, or the device will degrade. And, apart from all these factors, so, that makes it much more controllable; that if we can engineer all this aspects, we can somehow, technologically control the degradation of the, the polymer and followed by the processing also should be very, very controlled, to, to basically control, the overall temperature and the moisture uptake of the material.

So, processing has to be done in a very controlled atmosphere, with a very limited humidity, or very controlled humidity. And, apart from that, we need to sterilize the overall device, so that, that can be used successfully, and as well be stored under refrigeration, so that, if the device has to be kept for certain idle time, that can be used after certain duration. So, basically with this, I end my lecture here. Thanks a lot.