Medical Biomaterials
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Lecture – 09
Biodegradation and Bioresorption

Hello everyone. Welcome to the course on a Medical Biomaterials. We will continue on the topic of Biodegradation and Bioresorption. As I mentioned biodegradation happens when polymeric material degrades into macro molecules, but the macro molecules can migrate, or they can remain in the body, so that is called biodegradation. So, a large molecular weight material degrades into smaller molecular weight material.

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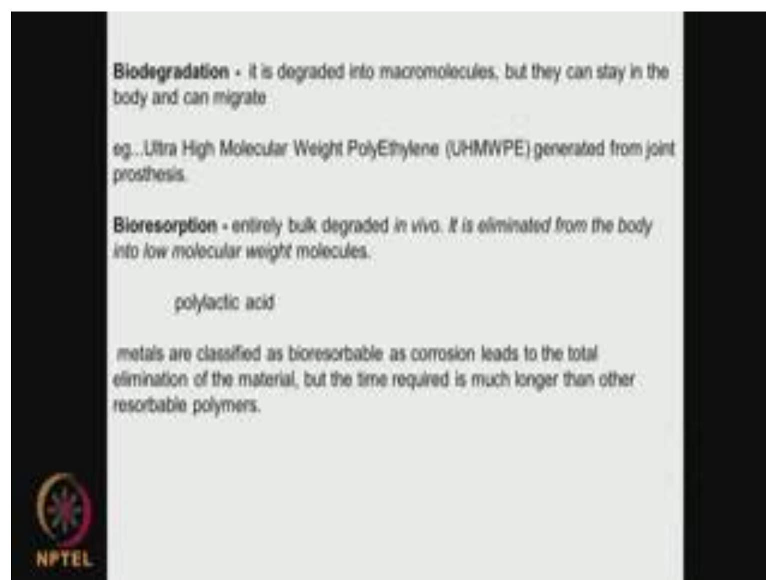

So, here we do not need to have the complete excretion of the macromolecule, whereas in bioresorption it is completely degraded and it is eliminated from the body into low molecular weight molecules. So, example of biodegradation could be ultra high molecular weight polyethylene, where we are talking molecular weight of 90000 or even 100000 Dalton. So, it may degrade into smaller molecular rate material and the material may stay inside. Whereas, in the bioresorption we take poly lactic acid, it gets degraded into say small molecular weight, even lactic acids is formed which is completely eliminated from the body, so that is called bioresorption.

Sometimes we even call metals as bioresorbable, and corrosion or attrition of a meta joins, metal implants, then we get the acrylate material which may be removed from the body excreted from the body. So, this could be much longer time; whereas, we take poly lactic acid it may be happening much faster when compared to. So, these are two important properties the biodegradation and bioresorption.

Nowadays, there is lots of lots interest in cardiovascular stents, can we have a bioresorbed cardiovascular stents. Currently they use titanium based alloys and they remain inside the body for ever. So, can I have a bioresorbable stent, after a few months starts completely disappearing? Can I have bioresorbable or biodegraded orthopedic implants? So, currently they use stainless steel or tyrannical titanium type of alloys which remains inside the body, and which remains with the bone. Can we have biodegradable or bioresorbable implant which will completely disappear once bone has really regained its strength? What about bioresorbed or biodegradable drug delivery system. So, a polymer encapsulated drug is introduced into the body, the polymer gets degraded and the drug gets released. So, in all these situations it is very important to have this particular property.

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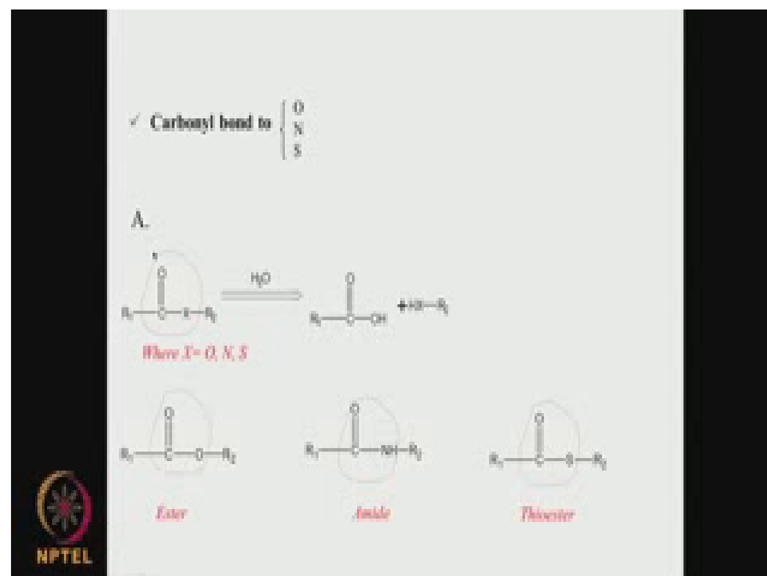

Generally there are certain bonds or bond systems which help in the degradation or resorbtion. So, you need to know those, so that when you are designing polymer polymeric blends you can think of having that sort of material. For example, if we take

say ester bond C double bond O O, this is called an ester bond, or if we take an amide bond C double O N H or if we take Thioester bond C double bond O S. So, they are easily and degraded either through hydrolysis or enzymatic hydrolysis or acid catalyst hydrolysis. So, these are very facile systems that are one thing.

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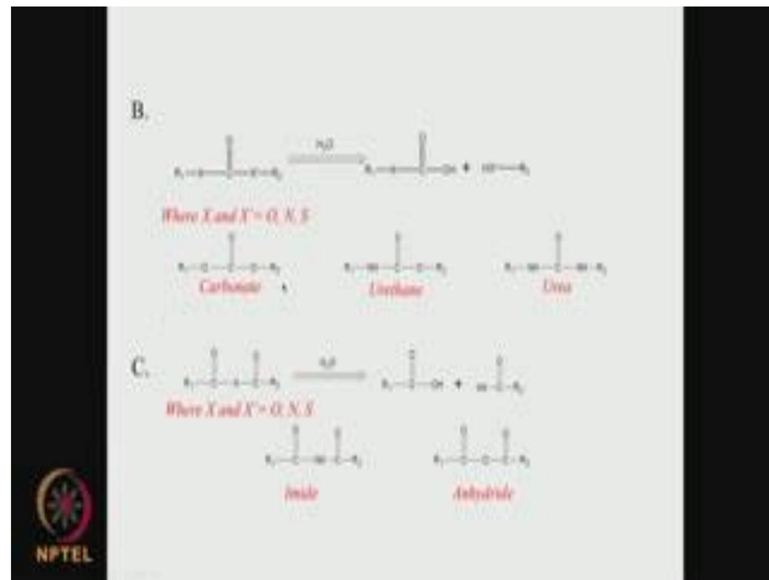

Another system where we have carbonates; so we have carbonates C double bond O and we have ether linkages on the either sides, or urethane. We have a C double bond O one side is O another side is N H or urea. We have C double bond O N nitrogen, nitrogen on both sides. So, these are also degradable. Let us look at another system imide. So, we have nitrogen both sides ketonic, or we have oxygen both sides ketonic. So, this is also very facile. They can easily degrade through hydrolysis. So, if you can introduce these types of bond systems in your polymer, you can expect them to degrade or desorbed.

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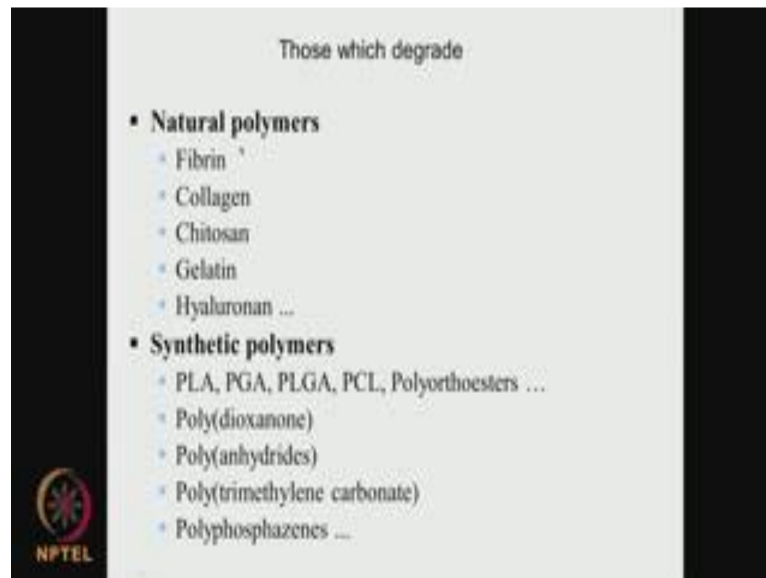

So, many polymeric systems degrade natural polymers or synthetic polymers. Natural polymers like fibrin collagen chitosan gelatin and hyaluraonic systems, or glucon, cyclodextrins, they all are natural which can degrade, synthetic like a poly lactic acid, poly glycolic acid, combination of poly lactic glycolic acid poly caprolactone polyorthoesters polydiaxanone anhydrides trimethylene carbonate, polyphosphazenes. So, all these are polymers which can also degrade. So, I can have here a blend made up of a degradable polymer and undegradable polymer. So, degradable polymer can have the drug which can get slowly released.

So, I can think of it about different types of strategies, by incorporating these biodegradable or bioresorbable materials into the design of biomaterial.

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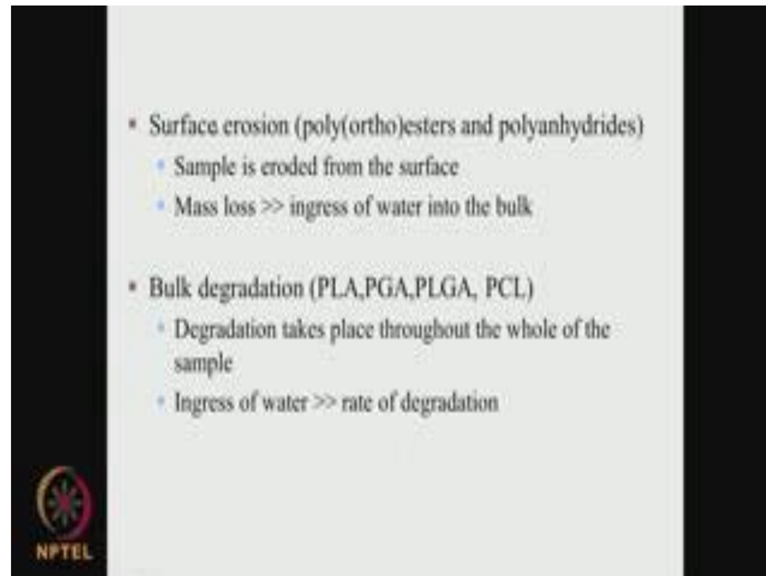

So, I also mentioned surface erosion; that means, material gets eroded slowly on the surface or bulk degradation. So, in the bulk degradation may be water ingresses very fast, and then the degradation happens. It could be acid catalyzed, hydrolysis or auto catalytic type whereas, in the surface erosion the mass loss, is much faster than the ingress of water into the bulk both types of systems have their advantage and disadvantages; surface erosion the material will become thinner and thinner. Bulk degradation material can one day completely disappear that is the bulk degradation. So, surface erosion polyorthoesters and polyanhydrides, bulk degradation we have poly lactic acid polyglycolic, PLGA, PCL and so on.

And also we have certain minimum thickness, if we have the thickness much less than that then you are going to, you can expect bulk degradation if you have very thick material, chances are you can have a surface erosion. So, we can think about both these type of a mechanistic approaches.

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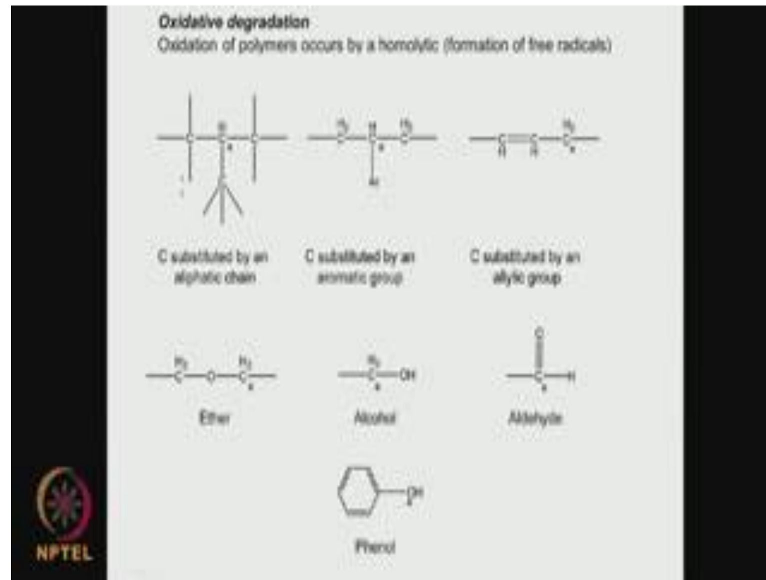

Then we also have oxidative degradation, many cases we talked about hydrolysis characterized by catalyst like acid or base or enzyme. We can also have oxidative degradation, their oxidation of the polymer curves by a homolytic or it could be heterolytic. So, in hemolytic; so we form radicals, free radicals. So, we can have a free radical formed here, this can happen when a carbon substituted by an aliphatic chain or a carbon substituted by aromatic, or carbon substituted by allylic group; that is C double bond C group or aliphatic like this or aromatic, or we can have situations like ether and alcohol or aldehyde or phenol. So, all these places there could be formation of free radicals, because of the oxidation or heterolytic.

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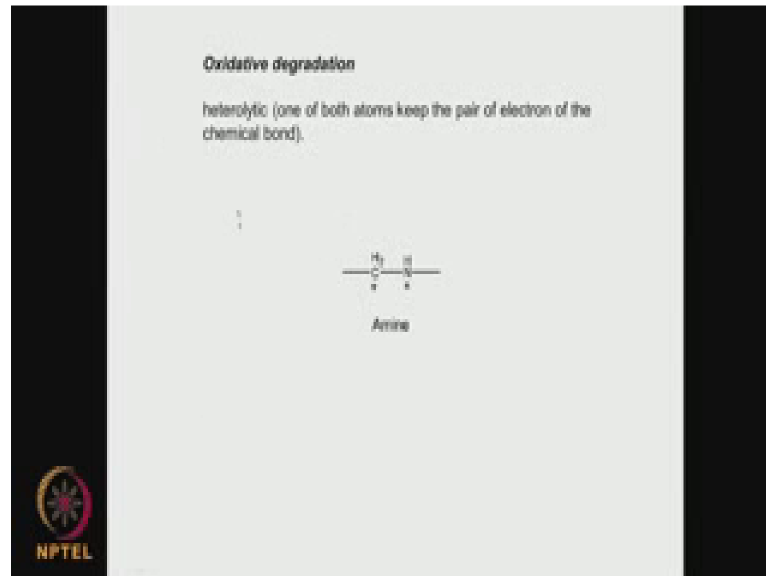

Where one of both the atoms keep the pair of electrons of the chemical bond. So, we can have two free radicals formed, especially in the case of amine. So, these are oxidative degradation.

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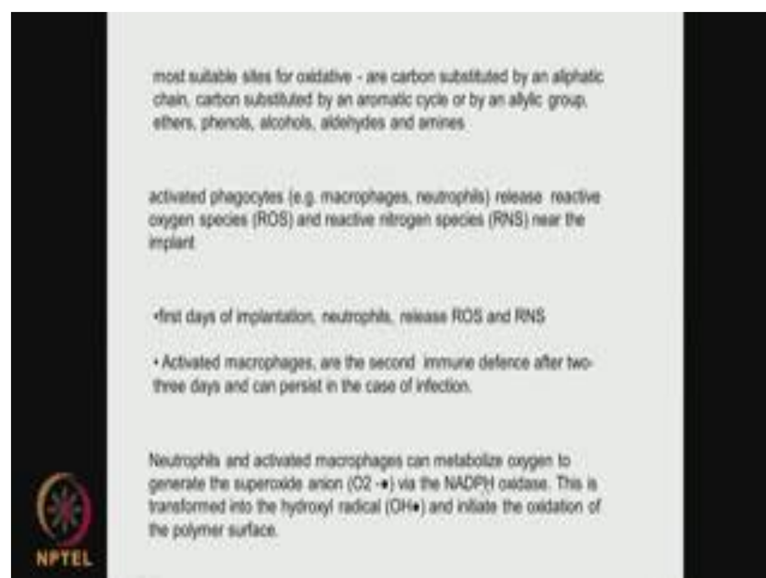

So, most suitable sites for oxidative are carbon substituted by aliphatic chain carbon substituted by aromatic, or by allylic group ethers phenols alcohols aldehydes amines. So, all these are locations for oxidative degradation. So, activated phagocytes; that means, macrophages, neutrophils release reactive oxygen species, these activated

phagocytes in the inside the human body, and reactive nitrogen species near the implant because they start attacking the implant, because the implant is seen as a foreign body. So, they are phagocytes. So, they release reactive oxygen species and reactive nitrogen species.

So, first day of implantation, almost 24 hours 36 hours neutrophils are released, and after a longer time macrophages are released actually. So, the first day of implantation, neutrophils are released. So, they release ROS and reactive nitrogen species. Now later on the activated macrophages they are the second line of immune defense, which happens after 2-3 days in case there is an infection. So, as soon as an implant is placed inside the body, these neutrophils release ROS and RNS. So, they can start oxidizing your implant. Then after sometime you have activated macrophages, they also, they are the immune defense system, they also start releasing these reactive oxygen reactive nitrogen species.

So, neutrophils and activated macrophages can metabolize oxygen to generate the superoxide anion via the NADPH oxidase, which is transformed into the hydroxyl radical and initiate the oxidation of the polymer surface. So, both of these; initial stages we have neutrophils released, later stages macrophages activated macrophages are released. So, they metabolize the oxygen, to generate the superoxide anion through the NADPH oxidase, which gets transformed to OH dot, which can oxidize your polymer. This is how oxidation takes place.

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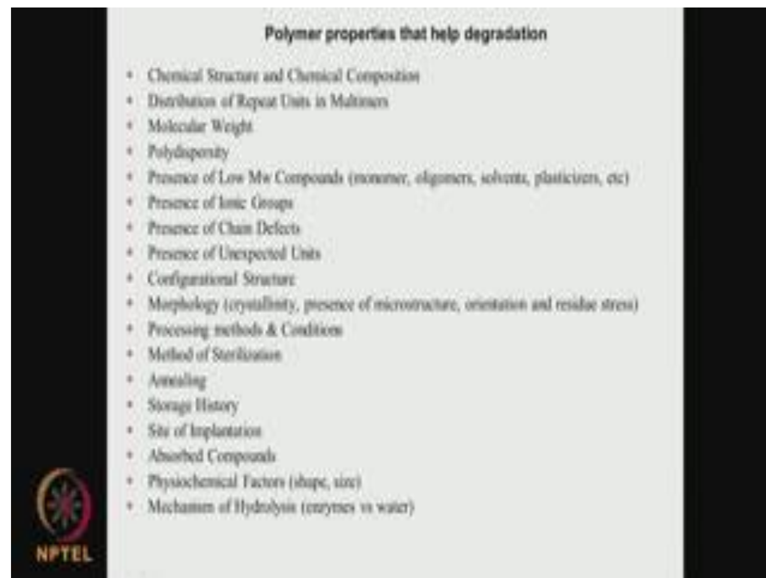

So many properties of the polymer which help in degradation; like the structure composition, distribution of the repeat units in multimers- the molecular weight it may be more easy to degrade smaller molecular even compare to larger molecular. Polydispersity: if you have a very polydisperse material, there will be a lot of smaller molecular weight material which may get dispersed. Presence of low molecular weight compounds, monomers, oligomers, solvents, plasticizers, they may get degraded faster, because plasticizers are very low molecular weight.

Presence of ionic groups, when you have ionic group you are going to have minus and plus charged on the surface, which may help in some of the acid catalyze or base catalyze reaction, presence or defects in the chain, presence of unexpected units, configurational structure, morphology; like crystallinity, presence of microstructure, orientation, residual stress, if it amorphous. Amorphous materials are easy to get oxidized or hydrolyzed, whereas crystalline structures are more difficult processing methods and conditions. How your process state how did we sterilize the material, how did we anneal the material, storage history, how long a storage, under what conditions site of implants, where you are implanting the material, because if you want macrophages neutrophils to be present.

So, you may have to have a blood region; if you are talking about hydrolysis through esters, or lipase, or that sort of enzyme. So, site of implantation plays a very important

absorbed compound, what type of material gets absorbed on of your implant. What are the physiochemical factors like shape, size, and mechanism of hydrolysis? Is it enzyme catalyst or is it acid catalyst or base catalyst, those things also. So, lot of properties effect the degradation of your biomaterial.

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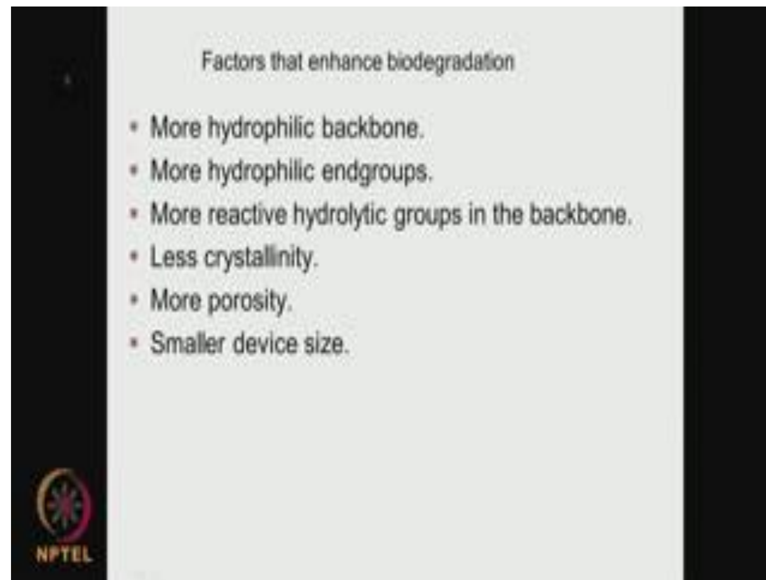

So, what are the factors that enhance more hydrophilic backbones will enhance degradation; more hydrophilic end groups also can enhance degradation, more reactive hydrolytic groups. Groups which can easily react with water, like I mentioned N H esters, they are all more reactive hydrolytic groups. Less crystallinity; that means, if you have more amorphous material, then it can degrade faster when compared to crystalline material. More porosity, you have more pores water ingress can happen. So, the reaction of hydrolysis can take place. Smaller device size, smaller material can degrade faster, because they can get attack from all directions when compared to large material.

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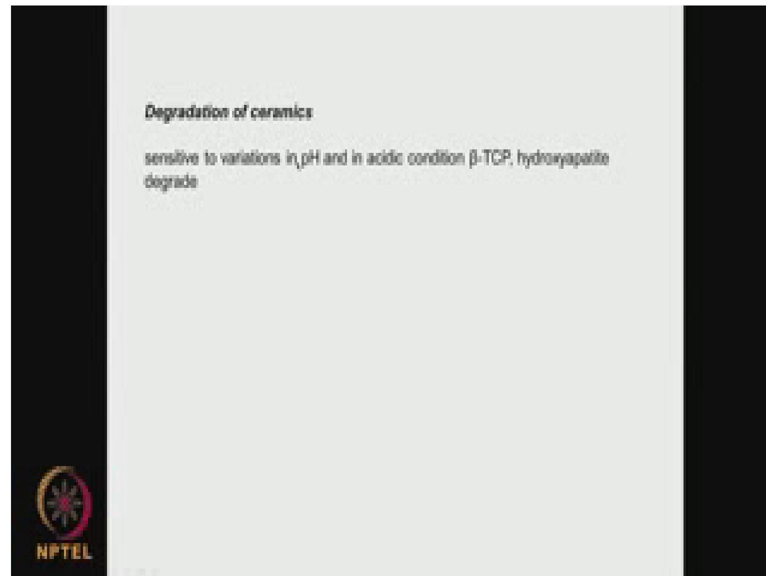

When you take about ceramics, they are also sensitive to variation in p h. So, in acidic conditions, like calcium phosphate, hydroxyapatite all these are bone implant, even dental implants they can degrade. So, acidic p H can be really detrimental ceramic material. So, you need to think, if you are having situations in, like where the p H is very low can I use ceramics, or should I use go for something else.

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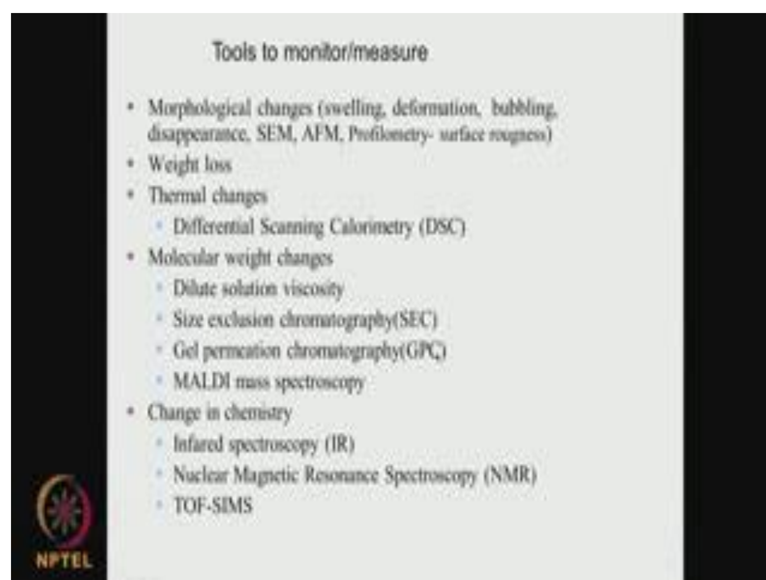

There are many tools we can use to monitor and measure degradation. We can look at morphological changes; that means, does the material swell, is they are deforming, is

they are bubbling, material disappear. Can I look the morphological changes using a scanning electron microscope? I can look at the morphological changes using atomic force microscope, or I can look at the surface roughness, because of degradation using profilometer. I can look at the weight loss of the material over a period of time, because if it is starts degrading, slowly the material weight will decrease.

I can look at the thermal changes using something called differential scanning calorimetry or calorimeter which tells you, what is happening to the physicochemical properties. I can look at molecular weight changes. If the material is degrading from polymer to oligomer, material must become smaller molecular with. I can use as viscosity as a measure, I can use size exclusion chromatography as a measure. I can use matrix assisted laser desorption ionization spectroscopy. So, I can measure the mass using this mass spectrometry. I can measure the molecular weight using size exclusion chromatography or gel permeation. If there are changes in the surface chemistry, I can use infrared spectroscopy or nuclear magnetic resonance spectroscopy or time of flied, secondary ion mass spectrometry techniques. So, many different tools I can use to check what is happening.

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Now, we can consider this polymer degradation as it is following as pseudo order. So, we can say the molecular weight at as a function of time could be molecular weight initial e power minus lambda t, This is a first order kinetics exponentially decaying right.

So, this lambda is a degradation rate, based on weight average molecular weight, for all the hydrolysable elements. So, if polymer has hydrolysable or non hydrolysable, will not consider the non hydrolysable portion, only the hydrolysable portion applicable when the polymer matrix in the initial stage has no macroscopic pores, because if it has got pores we need to consider slightly different model. So, it is a bulk polymer and m naught is the initial molecular weight of the hydrolysable portion, lambda is the degradation rate constant t is your time. From this simple equation we can find how the molecular weight average molecular it goes down with time.

If it has got porosity with the initial porosity alpha, then we just change this equation to m t is equal to m naught e power minus lambda t plus t add, t add is logarithm of 1 minus alpha divided by lambda. So, how this equation is got is, at initial time it is got porosity alpha. So, if u you go in the negative time at some point, the porosity could be 0; that means, you have a solid bulky material. So, this t add is the time taken for it to reach from 0 porosity to porosity of alpha; that is what this is actually.

So, if the polymer and is bulky material, there are no pores. We can use this equation for determining the change in the weight average molecular weight as a function of time. If it is got a initial porosity, then we can use this equation to calculate the weight change in the weight of average molecular weight as a function of time. So, if I know the lambda, I can follow the molecular weight and we assume it to be exponential. This is based on this particular reference.

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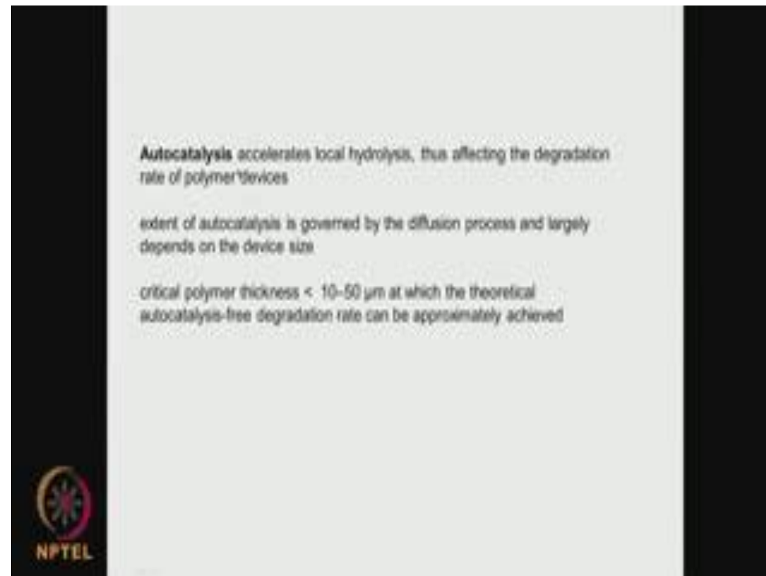

There is something called auto catalysis. Auto catalysis is initially the rate of degradation could be slow, as you keep forming some, may be acidic products or ionic products, and these may be catalyzing the reaction further and further. So, the rate of reaction may be picking up very fast. So, auto catalysis accelerates local hydrolysis, thus affecting the degradation rate of polymer devices. So, the extent of auto catalysis is governed by the diffusion process, and also it depends on the device size. And the critical polymer thickness should be less than 10 to 15 micrometer, at which the theoretical auto catalysis free degradation can be approximately achieved.

So, if you have very thin material, less 10 to 15 micrometer, then we can say auto catalysis may not be happening, but if you have thicker material, we can say auto catalysis can be happening if the degradation products are, like acidic, like if you take poly lactic acid, when it degrades it gives out lactic acid, which is acidic which may enhance degradation further and further. So, your rate of degradation picks up very fast. Initially degradation could be slow, then the rate picking up very fast; that is called auto catalysis.

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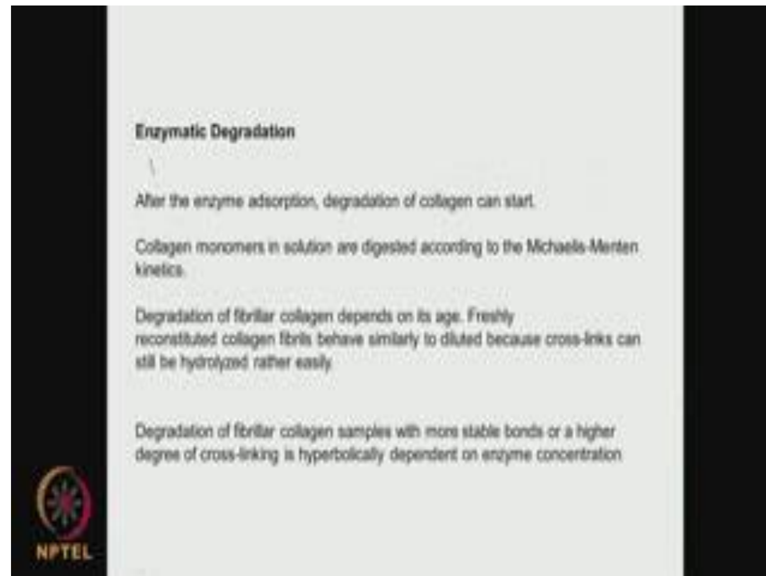

We can have enzymatic degradation, enzyme has to get absorbed, and then degradation can start, like collagen. Collagen monomers in solution are digested according to michaelis menten kinetics. You remember Michaelis Menten kinetics for enzyme reaction. So, degradation of fibrillar collagen depends on its age. Freshly reconstituted collagen fabrils behave similarly to diluted, because cross links can still be hydrolyzed rather easily. So, when it is freshly made, the cross links can be easily hydrolyzed like a, whereas if it becomes older and older, the cross link becomes very strong, then it is very difficult for you to degrade.

Degradation of fibrillar collagen samples with more stable bonds, or higher degree of cross linking is hyperbolically dependent on enzyme concentration. So, we need to have more and more and more enzyme concentration to degrade very old collagen, or if it is highly cross link, whereas newly collagen and if it is less easily cross linked it can be hydrolyzed. So, here we need enzymatic, whereas in the other one we have hydrolysis.

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Langmuir adsorption is combined with degradation
valid when adsorption is faster than degradation and desorption is the slowest step.

$$Vo = \frac{k[E_a]A}{[E_a] + 1/K_D}$$

k = degradation rate, $1/K_D = K_m$, Eo = E + Ea

not all adsorbed enzyme molecules must inevitably build an enzyme substrate complex (Ea≠ ES) because adsorption can also occur at sites which can not be cleaved

Enzymatic Degradation and Drug Release Behavior of Dense Collagen Implants, Iris Metzmacher, 2005

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So, if you are talking about enzymatic degradation, we not have the enzyme adsorbed and then degradation. So, we can assume langmuir type of absorption, combined with degradation, so where adsorption is faster than degradation. So, we can consider this type of reaction V naught, where V naught is the rate of reaction is equal to k E naught a divided by E naught plus 1 by k d, 1 by k d is equal O K m, K is the degradation rate, E naught is equal to the E plus E a, because enzyme may get absorbed on the polymer surface, but not all absorbed enzyme molecules must lead to enzyme substrate complex.

That means, not all the enzymes that gets absorbed will take part in the reaction, because there could be some enzyme which may be absorbed. But it is not going to hydrolyze the surface, because absorption can also occur at sides which cannot be cleaved. So, we may have on the polymer surface, some sides which may be cleavable, some sides which are not cleavable, but your enzyme may get absorbed in so many different places also. So, we need to consider those aspects here. So, we are talking about absorption and reaction on the polymer. So, we are considering langmuir absorption, and we are considering michaelis menten and type of reaction.

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Let us look at a couple of problems, very simple problems, but gives you an idea about what happens to degradation, because when you do degradation, you may increase pore size. When you do degradation the polymer strength also may increase. So, is it advisable, we need to consider, and whether the polymer strength goes down much lower than what is really you would like to have. An implant made up of a polymer with an initial porosity of 5 percent, is undergoing bioresorption; that means it is slowly disappearing. So, that its porosity is increasing like this you know. So, initial porosity is 5 percent. So, the porosity is decreasing as a function of time. So, there is some constant, this is called degradation rate constant. So, this is an exponential this is a equation obtained like this.

So, k N is the degradation rate constant, based on number average molecular weight, this is 0.02 per month, and this is got a unit per month, because you have time here right. The modulus of the dense polymer without any pores is 3.5 Giga Pascal; that means, without any pores. Calculate the modulus of this material after 5 years use Voigt model. So, modulus also very important, because this strength, tensile strength will change depending upon the modulus, and as the polymers starts degrading bioresorption so the porosity increase. So, the modulus will keep decreasing.

Now, the Voigt model states modulus of biomaterial is combination of modulus of air and modulus of polymer. The initial porosity is 5 percent, so modulus of air into .0 5. So,

we can neglect this term. So, modulus of polymer a into 1 minus 0.0 5, because 95 percent is material 5 percent is air; that is initial. So, when I put modulus of polymer here has 3.5, this is 0.95 I get 3.325 Giga Pascal, and this is the Voigt model. Voigt model assume it to be addition, linear addition. So, if we have porous material, we can neglect that porosity of that material, we take the remaining porosity and then multiply the modulus of the polymer to get the modulus of the biomaterial.

Now, there is a degradation so 5 keeps increasing, what is happening to the modulus after 5 years. So, porosity when t 61 5 years 5 into 60. So, we put in these terms 0.05, then this is 1 minus 0.05 into 1 plus exponent of minus 2.02 is this term into 60 minus two, into exponent of minus 0.02 into 60 that gives you 0.5139. So, you see the porosity has increased from 0.05 after 5 years it becomes 0.513. So, almost 50 percent of the material is porous.

Now, we need to put it in the voigts model. So, that 51 percent will not contribute to the modulus of the biomaterial, the remaining 49 percent will contribute; so the modulus of the biomaterial after 60 months. So, modulus of air into 0.5139 plus modulus of polymer into 1 minus 0.5139 that gives you 1.7 Giga Pascal. So, what has happened modulus of the biomaterial has gone down in 5 years from 3.3 Giga Pascal to 1.8, almost half? So, is it desirable that is what we have to see? So, if we have a material and it is losing its modulus, so its strength is going down, so we need to see whether it is desirable or non desirable, so depending upon the type of application, type of situation and so on.

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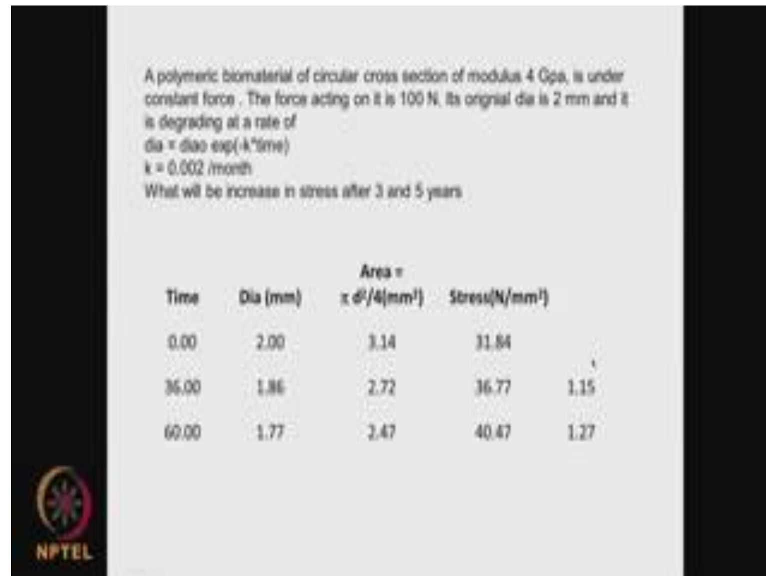

Let us look at another problem, a polymeric biomaterial of circular cross section of modulus 4 Giga Pascal is under constant force. So, especially may be in orthopedic situations. The force acting on it is 100 Newton, its original diameter is 2 mm and it is degraded at the rate of diameter equal to diameter exponent minus k into time, k is 0; 0 0 0 2 per month, so the diameter becoming smaller and smaller. So; obviously, cross section area is becoming smaller and smaller. So, the force acting on it is 100 Newton. So, it is got a 4 Giga Pascal, so; obviously, stress is going to change. What will be the increase in stress after 3 and 5 years?

3 years is 36 months, 5 years is 60 months, original diameter is 2 mm. So, diameter changes as function of e power minus 0.0 0 2 into 36, it becomes. So, the diameter has become 1.86 mm, whereas if it a 5 years that is 60 months. So, if you put here the diameter has become 1.7 mm. So, area is pi d square by 4. So, diameter is this, original area is 3.1 4 mm square, after 3 years it is become 2.72 mm square, after 60 months it is become 2.47 mm square.

Stress is Newton per area right; that is 100 Newton; the force is constant, whether it is 0 year or third year or fifth year. So, 31.84, force by area force is 100 by area stress, then force by area 100 by 2.72, force by area 100 by. So, the stress as you can see is increased from 31.84 Newton per millimeter square to t 8, 15 percent in increase in 3 years, 40.47 Newton per millimeter square. So, that is 27 percent increase in 5 years. So, the stress

has increased on the biomaterial at constant force in 3 years and 5 years, almost in 5 years it is gone up by 27 percent. So, we do not whether it is desirable or not desirable, will it cause any issues. So, you need to, see depending upon the situation where you have. So, in a places where this type of degradation is not desired, as you can see in this particular example, stress has gone up to almost 27 percent. So, we need to consider what to do if that is not desirable.

So in the past two classes we talked quite a lot about bio degradation and bioresorption, what type of functional groups enhance, and we looked at auto catalysis, we looked at bulk degradation and surface degradation. We looked at functional groups which lead to this type of biodegradation. Then we looked at very simple problems, but they are very useful for you understand. What can happen to some of the mechanical properties, when there is a degradation both the in the case of bulk as well as in the case of surface erosion.

Thank you very much for your time.