Drug Delivery Principles and Engineering
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Lecture – 60
Responsive Delivery Systems – II

Hello everyone, welcome to another lecture for Drug Delivery Engineering and Principles.

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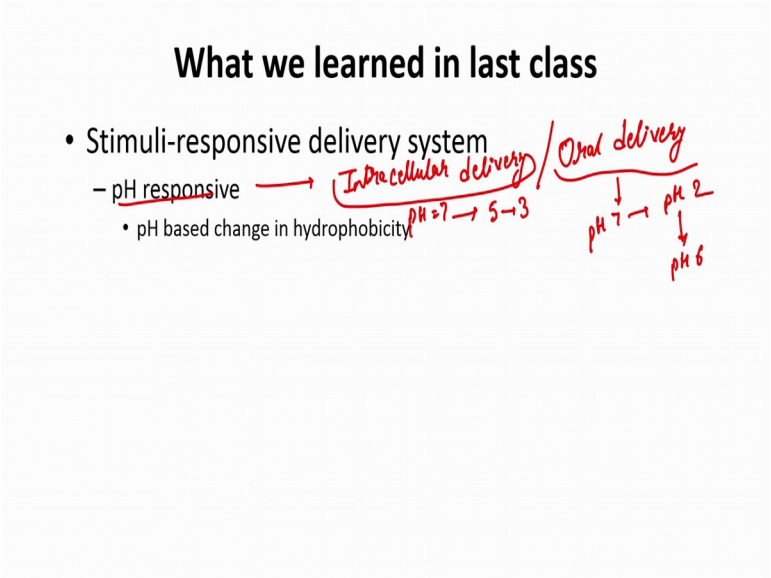

We have been talking about, stimuli responsive systems. So, let us do a quick recap of, what we learned in the last class. In the last class, we started with pH responsive systems. These are system that will responds to change in pH, mostly used for intracellular delivery; as well as oral delivery. And the major reason for that is where we see quite a lot of variation pH ranges. If we are taking something orally, we are going all the way from pH 7 to down to down to pH 2 And then back up to pH 6 or something.

And then similarly in the intercellular delivery, we are again going from pH 7 to pH 5 and then further down as the cell continue to send the cargo towards the lysosome. So, maybe down to even 3, that it goes down to. So, we can use this change in pH to cause trigger and change in the material that we have been using, and that is how it becomes a pH responsive system. So, in that, we first talked about pH base change in

hydrophobicity. So, we said that, what will happen is at a certain pH the polymer that we are using is going to become extremely hydrophobic, and because it is extremely hydrophobic it will then, if it is let us say encapsulated in an endosomal membrane.

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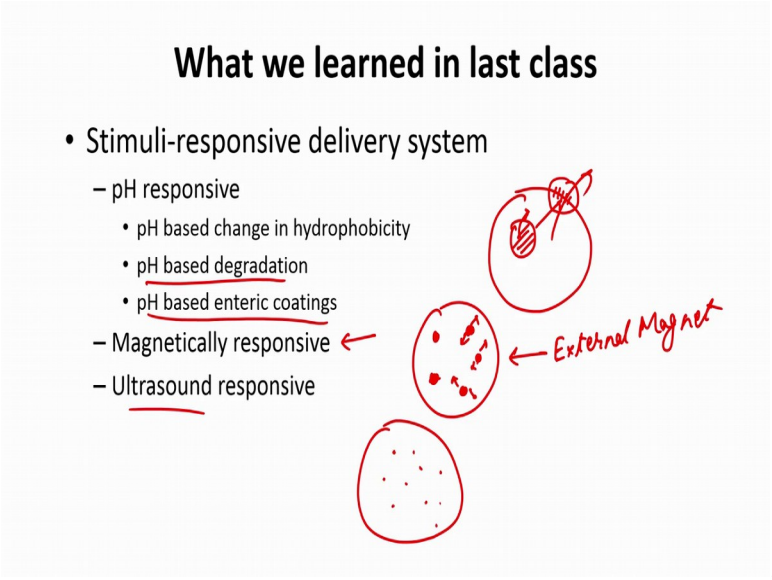

And this particle is becoming hydrophobic, then it will try to interact with these membrane bilayer lipids and it will cause disruption.

Once it caused disruption whatever is inside is going to come out. So, that is one way. So, more on inter cellar delivery, another one is pH based degradation. So, maybe this starts to degrade very rapidly at low pH and again this may expose components, which are hydrophobic that may degrade the membrane or maybe it is an even encapsulating some components, which are membrane degrading or membrane disrupting.

So, in that way again the endosome disrupt. And then last thing we talked about was enteric coating on the pH, which again we have discussed several times. This is a coating you coat over your oral tablets or oral delivery methods, which will remain insoluble at low ph, but will become soluble as the pH increases. So, basically protecting it at the harsh environment in stomach.

And then we discussed two other innovative systems; one was magnetic responsive. So, in this case, what was done is in a particle. They had encapsulated magnetic material. And these magnetic material responds to an external magnet. So, let us say, if it is in my

skin and if it goes and gives oscillating magnetic field over my skin and all of these will start to vibrate. And because of that, they will cause enhanced penetration of the solvent outside as well as enhanced diffusion of whatever was encapsulated inside this system.

And in a very similar concept, we talked about ultrasounds. In this case instead of using a magnetic material, we were using ultrasound as one of the mechanism and this relied on the fact that there are pockets of gases, in the system and these will caviate and burst and expand and because of that again very similarly, they will change the entropy in the system. It will cause enhanced diffusion of drug from inside to come out as well as solvent to move in. So, these were some of the systems, we discussed.

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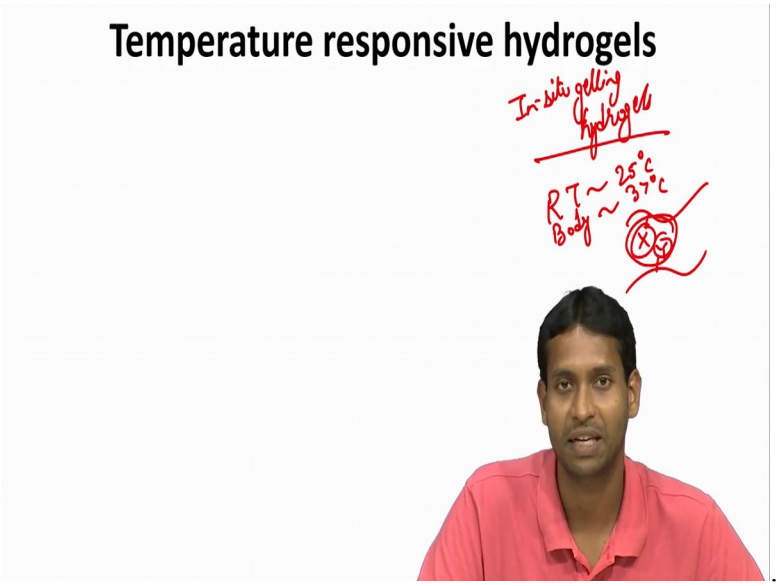

So, in today s class, we will talk about temperature responsive hydrogels. Again some of this we have discussed,maybe the polymerization gets triggered at a certain temperature. And we have talked about it in the context of In-situ gelling hydrogels; insitu gelling hydrogels. What were these; these were nothing, but the polymers that will form a gel above a certain temperature. Because maybe a chemical reaction starts at a certain temperature or maybe, it is at a much higher pace the reaction happens at higher temperatures.

So, maybe at room temperature, which is let us say is 25 degree Celsius. You have a reaction that is extremely slow. So, maybe you have two polymers with two functional groups X and Y which react to form a gel, but then X is X and Y reaction is slow at room

temperature, but once you injected in the body. The temperature has now increased to 37 degree celsius and then this can happen in a much faster pace. And you will have gelation happen at the site of injection. So, that was one thing, we have already talked about in terms of temperature responsive hydrogels

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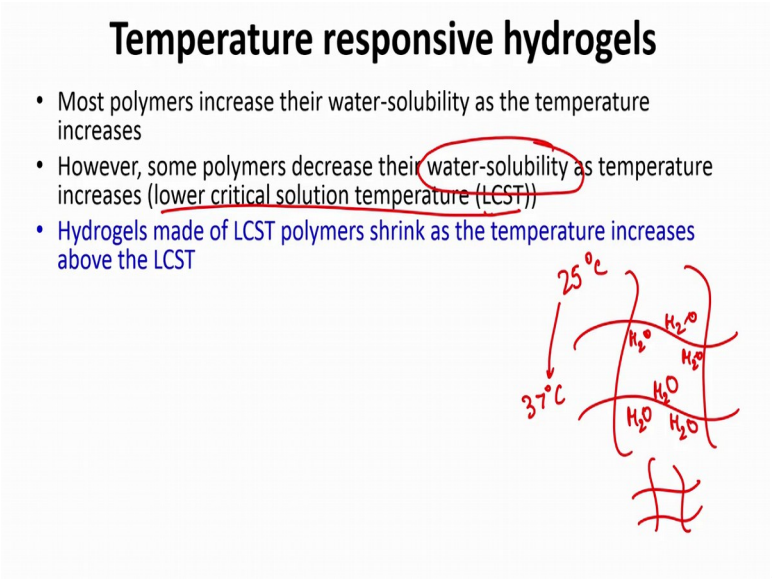

But, we will look at another property that is used in the literature. And before we go into that, I will just give you a brief overview, most polymers will actually increase their water solubility as the temperature increases. So, that is fairly obvious right I mean if you heat something up it tends to become more soluble. You give it more energy, it tends to interact more with the surrounding. However, there are some polymers that actually decrease their water solubility as a temperature increases. So, which basically means that as you heat them up, their solubility will go down. So, if they are already soluble and you heat it above a certain temperature, they will start to actually precipitate out. And such polymers are called LCST, which is lower critical temperature solution. So, LCST.

So, if I make hydrogels out of such LCST polymer, what will happen is. They will actually shrink as that temperature increases above the LCST. So, if I am saying the water solubility is decreasing and, let us say this is an hydrogel. So, this is at 37 degree Celsius. Now if the temperature is reduced; or let us say this is a 25 degree Celsius. Now the temperature is increased to 37 degree Celsius and everything the water solubility will decrease, then all this water molecule that was interacting with these polymer chain will

reduce. And because this is reducing, what will happen is this will cause this swelling to decrease.

And. So, you actually have these hydrogels that will actually shrink as a temperature is increased and it goes above a certain temperature, which is the LCST temperature.

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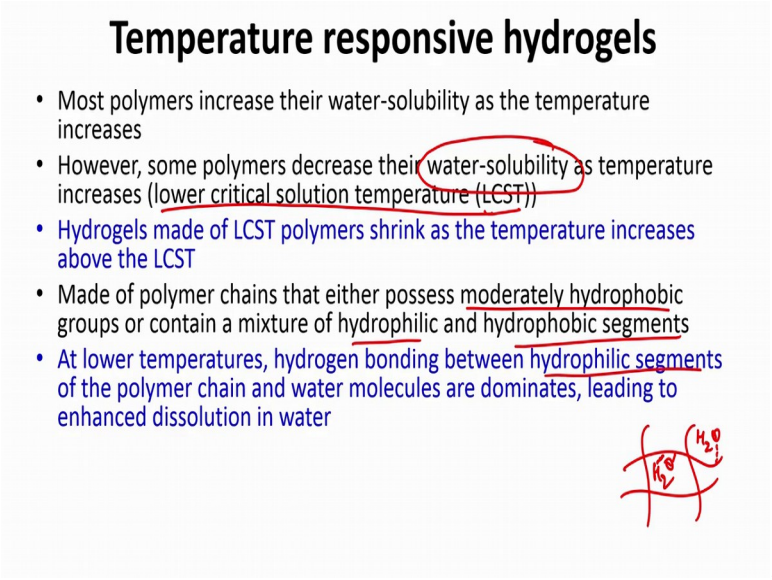

So, these are typically made from the chains, which moderately hydrophobic. So, they cannot be extremely hydrophobic in that case, its not a hydrogel remember the hydrogel is something that is extremely hydrophilic, but these particular hydrogels are made with something that are moderately hydrophobic , hence they contain a mixture of hydrophilic and hydrophobic segments.

So, as the as the temperature is decreased, the hydrogen bonding between the hydrophilic segments, that includes the hydrogen bonding with the water and the polymer that starts to go down. Because the temperature is being increasing, but the hydrophobic interactions, what is written here is actually the inverse. So, at lower temperatures this hydrogen bonding between the hydrophilic segments of the polymer will dominate. So, at low temperatures is going to interact with all these hydrogen bonds. And it will absorb more and more water. So, it will cause the enhancement of the dissolution in water as well as if it is a hydrogel and cause enhancement of swelling.

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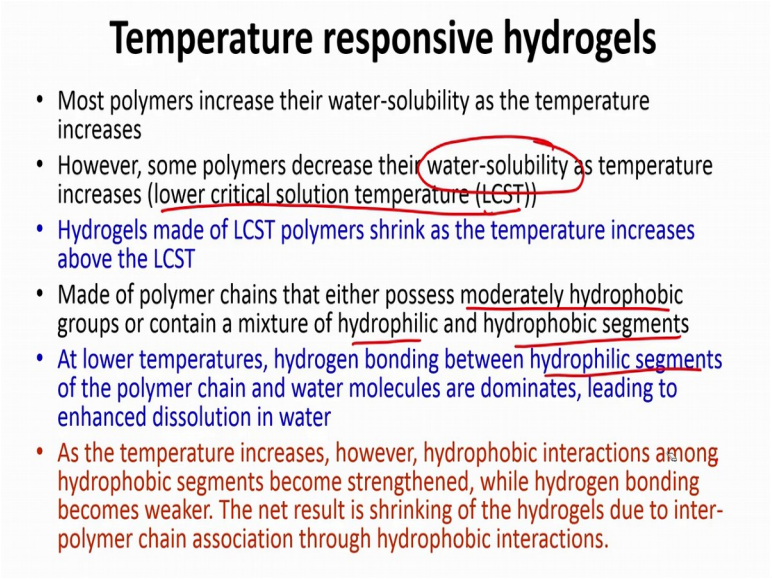

However, as the temperature increases, the hydrophobic interactions among the hydrophobic segments become strengthened. While this hydrogen bond which is fairly weak bond it starts to degrade. And it will become weaker. So, the net result is that the hydrogel is now interacting with the hydrophobic domain with other chains and not interacting with the water as a hydrophilic domain.

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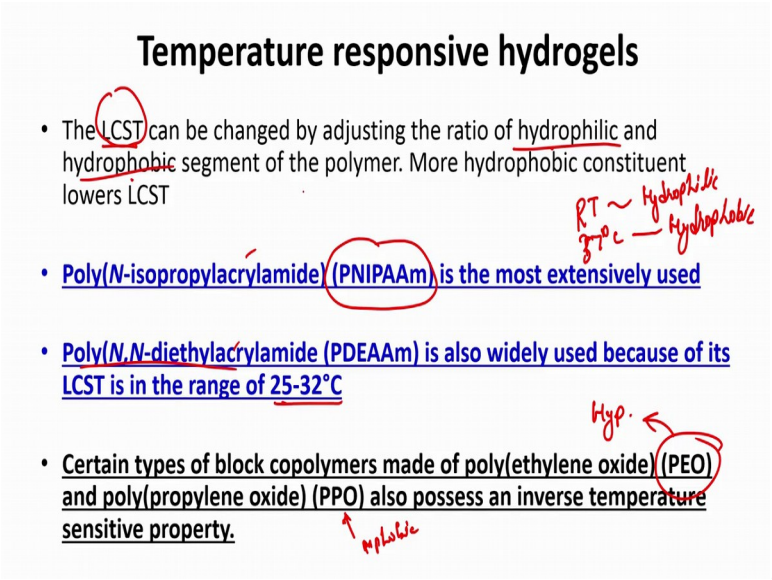

Hence it will cause a shrinkage of the polymer. And thereby the hydrogel. I hope this is clear now. We have already defined lower critical temperature and this can be adjusted by adjusting the ratio of the hydrophilic and hydrophobic segments.

So, you can have different types of polymers that are being designed that have various LCST depending on how much hydrophilic and hydrophobic domain that you were putting in. So, more is the hydrophobic domain, the lower is the LCST. One of the polymer that is widely used for this is poly PNIPAAm and the reason that is used quite a lot is, because it has LCST in the range of about this 25 to 30 degree celsius. So, here is another polymer the poly N, N diethylacrylamide. That also has an as LCST at 25 to 32 degree Celsius so; that means, that at room temperature, they are fairly hydrophilic, but as the temperature is increased to 37 degree Celsius the hydrophobic components dominate.

Certain types of block co-polymers can also be used. So, obviously, these molecules are both hydrophilic and hydrophobic domains, but you can have combined two polymers. So, one is PEO which is nothing, but PEG which is hydrophilic. And you can have PPO which is hydrophobic. And if you combine them you will cause this property also to have LCST.

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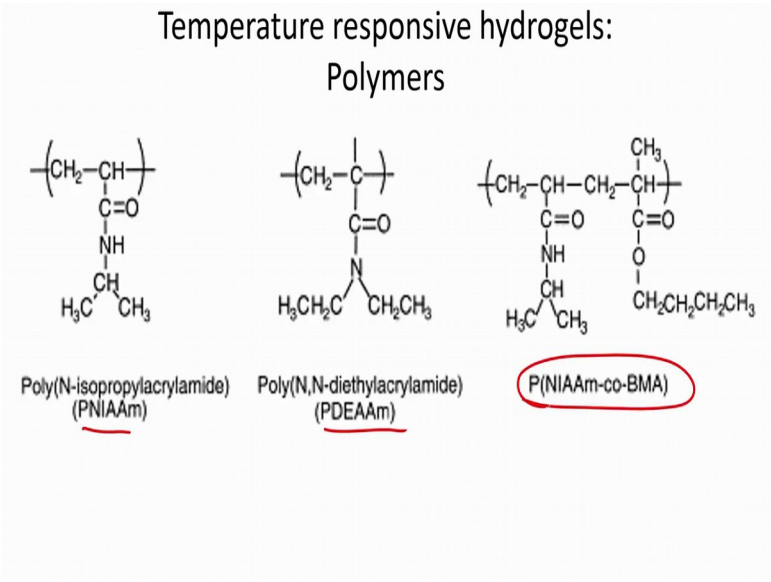

So, again here are some of the structures that you can see . you do not need to remember this, but just for your knowledge. So, here is your poly NIAAm, here is your PDEAAm and another poly NIAAm co polymer.

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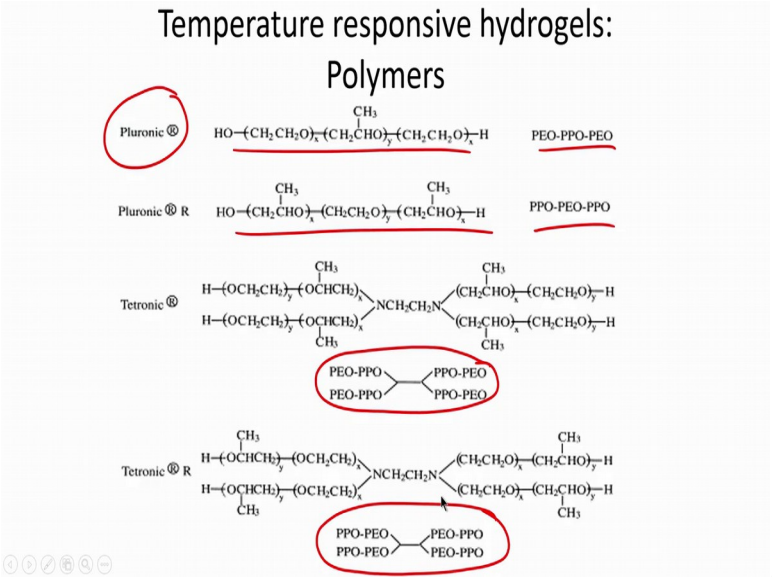

Here are more hydrogels that are being used. So, you must have heard of the name pluronic. That is used quite a lot in the field and here are some of the structures. So, these are nothing, but copolymers from hydrophilic and hydrophobic polymers that result in different LCST and different properties being attained by these polymers. And here is an example of how this can be used.

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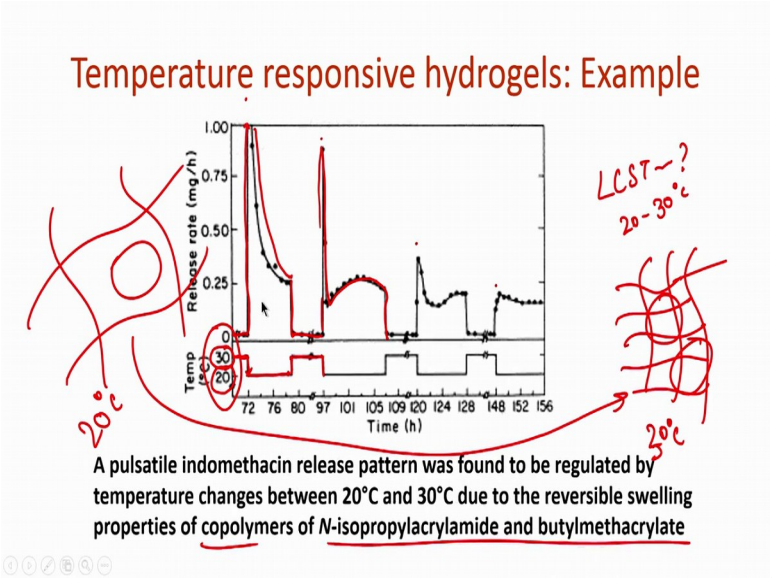

You have a polymer and you made a hydrogen out of this. You are then measuring even capsulate. So, encapsulated something and then now you are amazing that release of a certain molecule and. So, in this case what this paper is doing is. They have a certain release rate at a certain temperature the temperature here is maintained at 30 degree celsius. And oscillated between this 1320 so; obviously, the LCST will then be what? It has to be between 20 to 30 degree Celsius right because that is where it is causing the modulation.

So, 30 degree Celsius, this is fairly hydrophobic; that means, that the hydrogel will be fairly in a collapsed format. So, if a drug that is being put in is of a certain size, which is much in than pore size of this hydrogel then it will remain encapsulated. So, that is what you see for this period, but when the temperature is then reduced, this is now becoming hydrophilic. So, this actually expands absorbs more water and now this drug is much smaller than the pore. So it can come out. Y ou see suddenly the increase in the release rate, till there is maintained; obviously, the drug keeps coming out. And as you then increase the temperature back up it goes back down to no release, because it has now switched from this format to this format.

So, this is at 30 degree Celsius and this is at 20 degree Celsius and again if you maintain it at a higher temperature there is no release, but as soon as you go back down you have another release that happens. And the cycle can be continued, but obviously, in this case

it is important to note that the maximum release is getting decreased. As time goes on because more and more drug is coming out over time. So, your amount of drug in the hydrogel is decreasing, but you can do this for multiple cycles to be able to get different types of release.

And again you can change the polymer that you are using. So, in this case this is a copolymer between these two polymers, but you can change these molecules and that will change the temperature at which you will observe this property.

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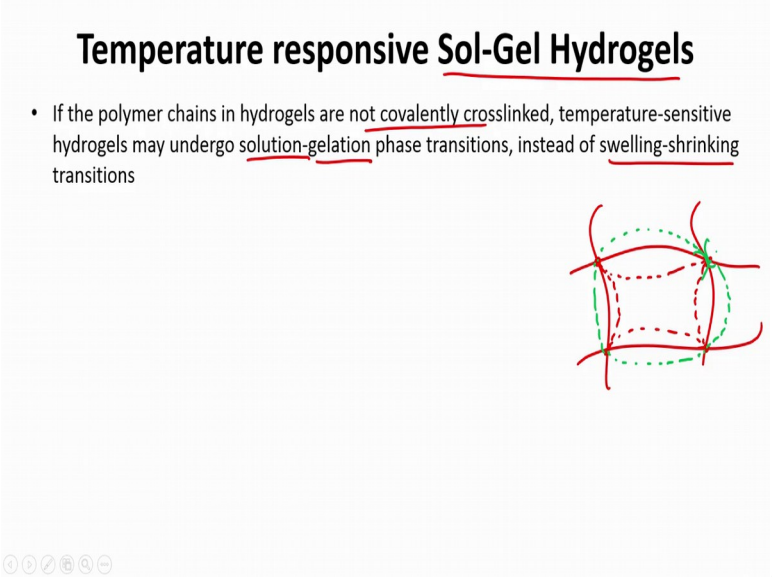

So, another variant of this is a Sol Gel Hydrogel. So, let us say the polymer chains and not covalently cross linked ah. So, in the previous case maybe they were covalently cross linked, this just as the polymer is becoming hydrophobic and hydrophilic the hydrophilic that is causing this, but in this case what are you saying is not covalently cross linked maybe it is physically cross linked.

So, then you can have an hydrogel that will switch between the solution phase and the gelation phase, instead of swelling and shrinking. So, swelling-shrinking is happening, because these polymer chains are obviously, tethered. So, you have these bonds being formed at this place. So, they cannot go anywhere. So, all you can have is a situation, where they either collapse like this. When they are hydrophobic they do not really want to interact with water or they can expand further like this. Where at this case they are hydrophilic and they are absorbing more and more water to be able to interact, but then

what if these bonds do not exist what if this is a physical cross linking. So, there is no actual bond they just tied up in each other.

So, in that case, what you will find is then this becomes either soluble or in gelation form depending on, what temperature is it.

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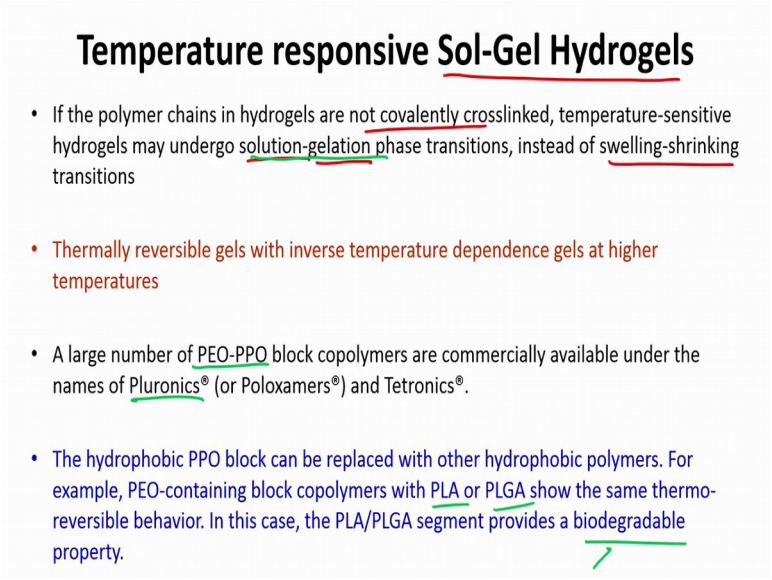

So, this will cause a thermal thermally reversible gelation. And it will have an inverse temperature dependence at a higher temperature; that means, at high temperatures they will become solution and at lower temperature they will become gel.

So, a large number of PEO and PPO block copolymers, that are commercially available including the pluronics are actually something that can have this sol gel behavior, with these temperature changes. The hydrophobic PPO block can be replaced with any other hydrophobic polymer. It does not have to be a PPO. So, for example, you can even replace it with the PLA PLGA fragment as well and this will again not only have the sol gel behavior, it will also give a biodegradable property. So, if you only use PP PEO PPO you have a non degradable; nonerodible hydrogel. In this case it will become an erodible hydrogel. If you use PLGA PLA because they can then cleave in presence of water.

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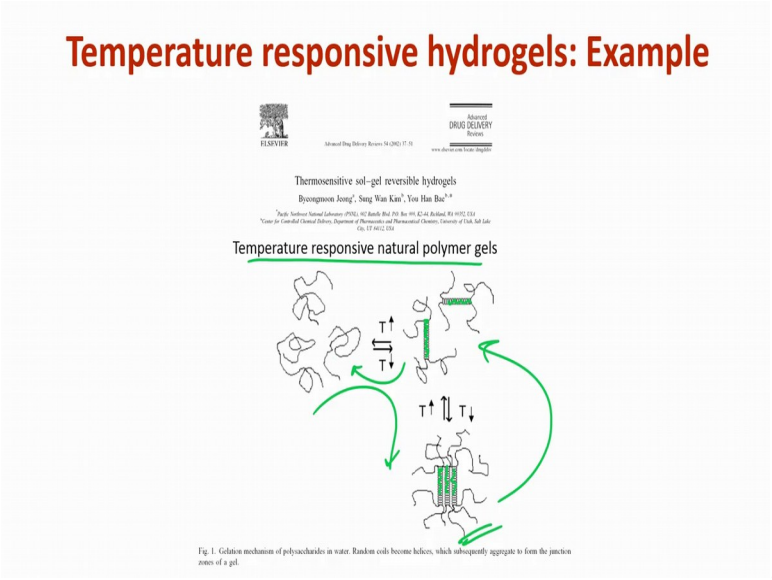

So, this is basically what will happen as the temperature is increased these chains are becoming more and more like this. And as the temperature is decreased they are starting to have these cross linking that is happening. So, you can play around and get a hydrogel at a certain temperature at a lower temperature and as you increase the temperature, further you actually have a soluble polymer because now this is fairly not interacting with each other.

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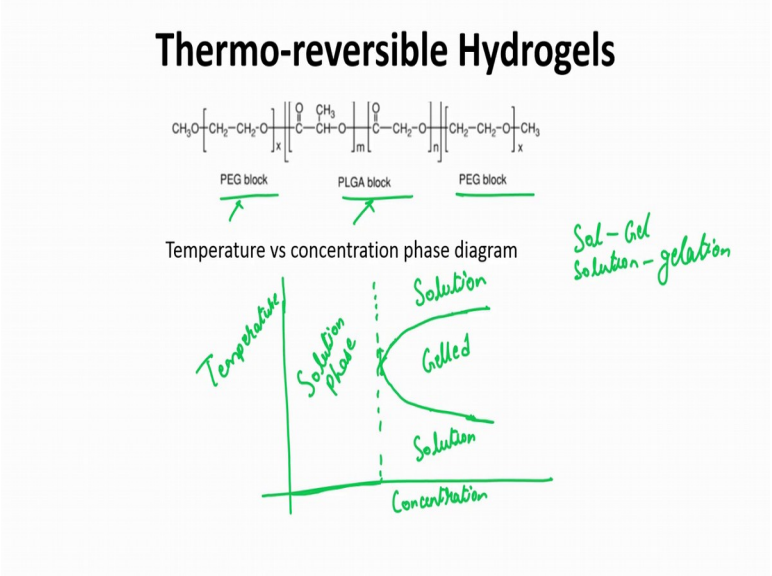

So, here is an example, this is a PEG block, here is a PLGA block, here is a PEG block again. So, this is PEG PLGA PEG and co polymer. And in this case you will find that this will again act as a sol gel, because it has both the hydrophilic and hydrophobic component and if I have to draw a temperature v ersus the concentration phase diagram of this polymer. So, when I say phase diagram, I am saying phase diagram between the salt and the gel phase. So, solution and gelation. So, now, if I have to draw this and let us say the Y axis is temperature, the X axis is concentration of your polymer.

So, what will happen at lower concentration? So, obviously, I need a certain amount of concentration for it to gel at all. So, at let us say it all the lower concentration, there is very little polymer around. So, that means, that it will all be in a solution phase. No matter what the temperature is. Now as the concentration increase and it reaches amount where it can form a gel depending on what the temperature is, what you will get is you will get let us say here is a point that at a certain temperature at a certain concentration it exist as a gel phase.

Now, if this is a sol gel, then as I increase the temperature and as the concentration is increased. So, at this point what I am saying is above this; this is solution below this is gelation. Now depending on what the concentration is as I further increase it. So, this is LCST as I further increase it, you will get a curve like this. Where at any concentration it can exist as a solution phase, it can exist as a gelled phase and then if you increase the temperature further again, it will even be able to break all these interactions and this will be again soluble phase. So, this is a typical phase diagram that you will get for your sol gel polymers.

And once you have this defined you can then just use some of these phase diagrams to determine what concentration, what temperature to use for a particular application. So, I hope this is clear.

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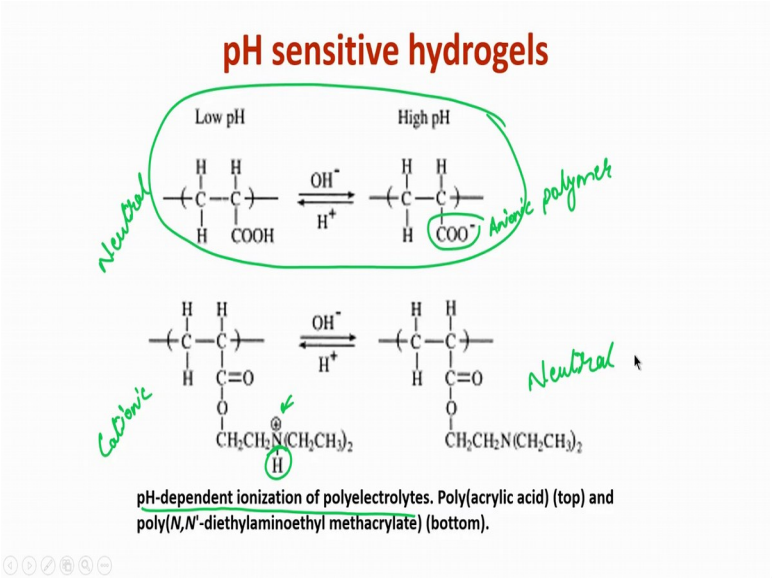

Next thing we can talk about this again pH sensitive hydrogels in this case it is going to be slightly different. So, we are talking about. Now release from the hydrogels on the basis of the pH. Some of these is p basically the major concept is the pH dependent ionization of the polyelectrolyte. So, we have already talked about this COOH thing. We are at a high pH this will lose its proton and existed in an anionic polymer and at the lower pH this will be neutral.

Similarly, you can have other amine based molecules and they will have inverse of this. So, as the pH is decreased, they will get protonated. So, they will become cationic polymer. So, here is your proton that is come in extra and they said here and then as you increase the pH, they will become neutral. So, both of these can be easily modulated in terms of the charge because of basis of pH and so, now, here is an example of how this could be used.

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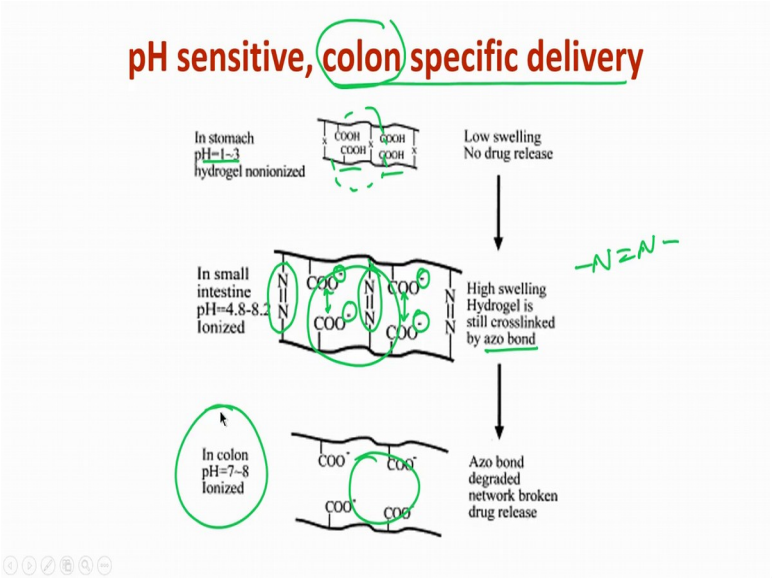

So, we are talking about colon specific deliveries. So, we are saying that we only want to deliver things in colon. And now if we give it orally, what will happen is the pH is fairly low. So, we have used these carboxyl containing polymers. So, since its pH is low this is neutral you have a certain pore size maybe your drug is quite big maybe this is the drug and it cannot really diffuse out.

But as the pH increases, the carboxyl groups becomes deprotonated because of this ionic interaction also. So, this is a repelling force, now that will happen the electrostatic repulsion. This will increase the pore size and so, now, maybe your drug molecule you come out.

So, if you want to deliver to a small intestine, this might be enough, but what further can be done is you can then also have another cross linking that is present which is this Azo bond the N double bond N and this bond is actually cleavable by some let us say colon specific enzymes. So, once it goes there, then you have these further increment in the pore size or maybe that polymers will completely fall a part. And at that point you can help release only in the colon. This is just one example of how these pH sensitive hydrogels can be used for different applications.

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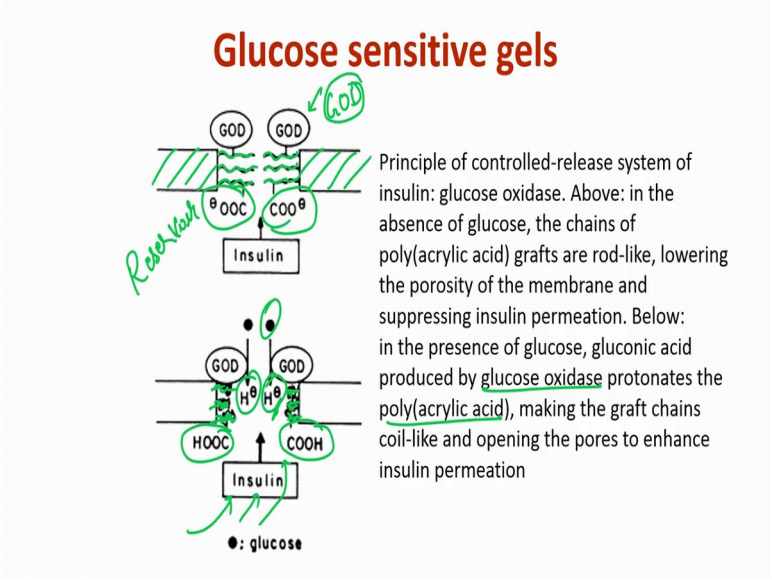

So, now here we have a glucose sensitive gel. So, let us see how this works. So, maybe there is this assembly, where you have some kind of a membrane. That has conjugated with some polymer which extremely hydrophilic and so, because it is hydrophilic it will tend to interact. The pore size is low and then since this is all expanded it is not letting anything to go in and out.

So, here is your reservoir of insulin. And what do you have also done is you have put in an enzyme called GOD, which is nothing, but a glucose oxidase. So, and then these polymers are nothing, but polyacrylic acid. So, now, because they are polyacrylic acid, they contain lots of carboxyl. So, as if the pH is high, they are going to be ionically charged, and they are soluble. So, that is why they can spread around, but if the pH is low, they will become neutral their solubility will decrease and they will then tend to not interact with water actually try to go back to the surface.

Now, since that has happened. Because they are no longer blocking this pore, the pore is opened and so, the insulin will come out. So, why would the pH decrease locally? So, that is because this enzyme GOD glucose oxidase is there. So, what will happen is in presence of glucose; this glucose oxidase will produce these H plus ions. And as these H plus ions are produced, the local environment the pH has reduced. Because the pH is reduced, you have now these polymers that have got protonated and they are no longer soluble, and as they no longer soluble they have just tried to avoid water and just instead

of having in an expanded form they have shrunk and attached to the surface and because of that now the insulin will come out. So, it is a very ingenious system where now glucose itself has equal concentration of glucose increases you have more and more insulin come out. And when the concentration of glucose decreases this H plus will also decrease. And then this will go back to its non protonated state causing blockage of insulin.

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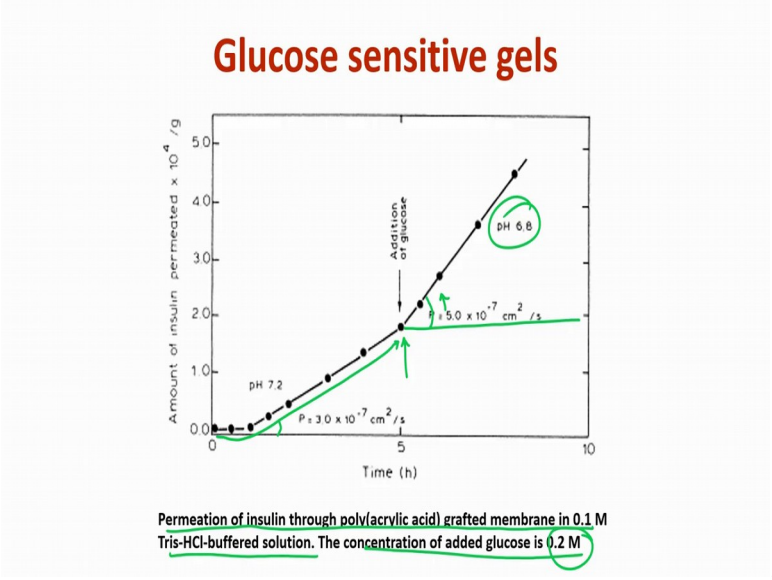

So, it is a system that is going to self regulate itself. So, here is what we see obviously, the system as I described it looks fairly, fancy and fairly good, but in practice when they see it says what they see they seem permeation of insulin through this membrane. In 0.1 molar HCL-buffered solution. And they have added quite a high concentration of glucose as well, which is 0.2 molar at a certain point. And you are measuring the amount of insulin that is being released.

So, as you can see over time, you see some basal level of insulin coming out. So, this is a certain slope, but as you have added more glucose. You see that the slope has increased. And that shows that the system actually does work the local pH has reduced to pH 6.8 because of this GOD enzyme and, but again its not very suitable in that regard. Because using extremely high concentration of glucose and the change in the slope is also not very significant, but nonetheless if worked upon you can have more systems like this that can be even more controlled and even more tunable.

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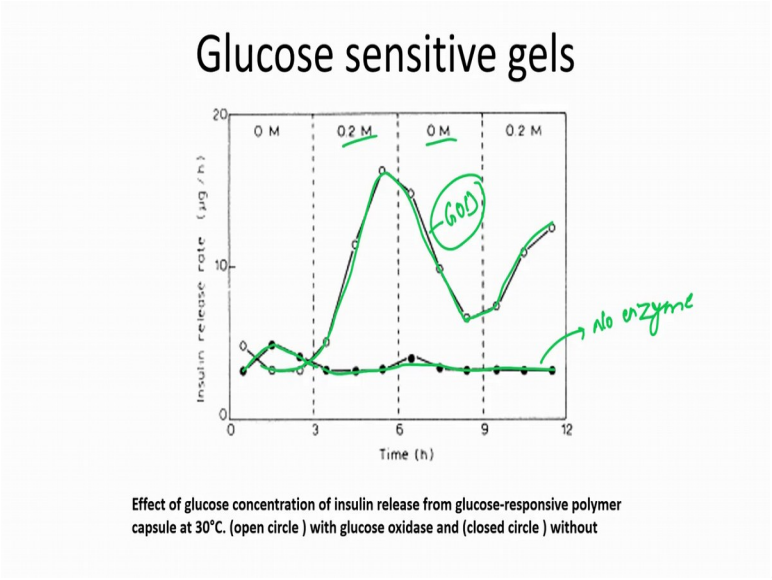

Effect of glucose concentration of insulin release from glucose-responsive polymer capsule at 30°C. (open circle) with glucose oxidase and (closed circle) without

So, here is further data on that. Not only you can have one cycle that was shown in the previous graph, but you can have it on the multiple cycles. So, here is what you see is, you have you have a polymer that either contains that glucose oxidase or does not. So, these open circle they have the GOD enzyme attached to it.

The closed circles have no enzyme and so, what you see in case of; in case of this there is the insulin release rate has a certain release rate which does not change in the presence or absence of glucose, but in the case where you have god enzyme. You see that there is a shift in the release rate as you increase the glucose level and once you go back down it goes back down and then the same cycle can be repeated.

So, it again shows that the system is tunable and you can use it for multiple times. Obviously, the concentration of the insulin release in the rate at which it is being released is going to be different, because you are also exhausting the reservoir as the time further goes up.

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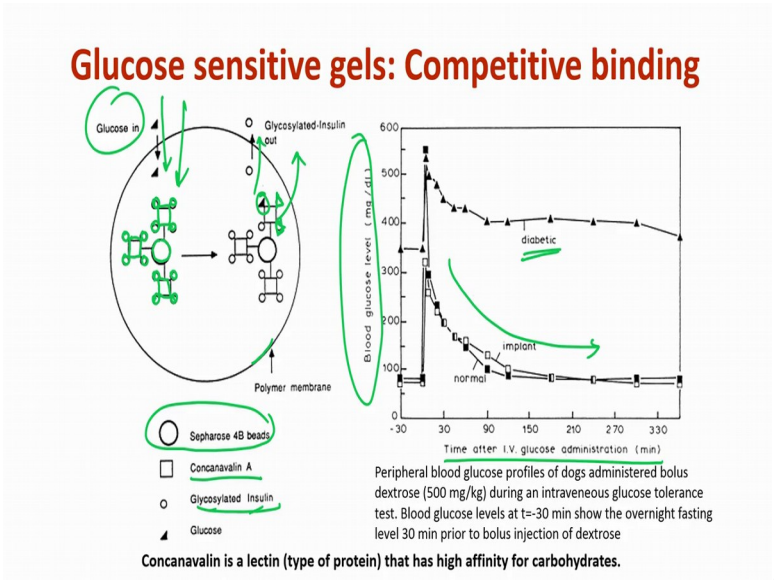

Then you can also have glucose sensitive gels with competitive binding. So, in this case what you are looking at is a polymer membrane. And in that you have put a sepharose bead that is conjugated to a lectin, which is in this case is a concanavalin A. So, here you have a sepharose bead to which you have attached a lectin; the lectin typically binds to carbohydrates with very high affinity.

And in this then you have put a Glycosylated Insulin. So, each of these lectin is now in this figure has been shown to be attached to 4 molecules of insulin. So, now, if a glucose is high in the serum. So, the body needs some insulin and then, because it is high in the concentration more and more glucose will come into this, as the glucose comes in it is going to competitively bind to this insulin which is glycosylated. So, it will replace this insulin by binding to your site at the lectin and it will competitively kick out insulin. And as the insulin is getting kicked out it will then come out and come in the system to then decrease the blood glucose level.

So, again very similar to previous example, this is a self regulated system. So, there is more glucose; more glucose comes in, as more glucose comes in it replaces more and more glycosylated insulin. And in that way you have more and more insulin coming out in the system and as the glucose will decrease this will rate of this will also decrease.

So, here is some data on that. So, you have blood glucose level on the Y axis and you have the time after the glucose was externally administered and. So, what you see is in in

diabetic folks, you see quite a high blue blood glucose level, but if you do put an implant in it and then you see that that glucose level comes down. So, thereby showing that this is a functional system.

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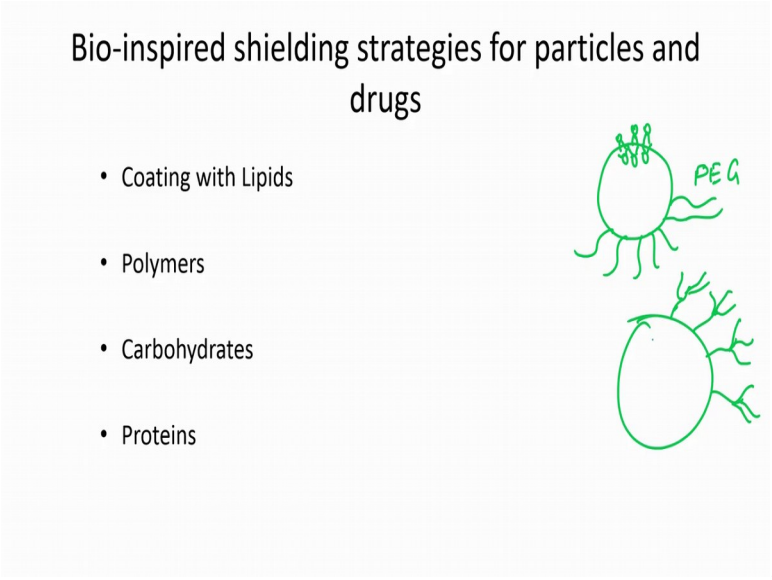

And then one final thing that I will talk about is the bio inspired shielding strategies and particles and drug. So, some of the inspiration of this comes on from the nature itself. So, you can if you have a particle you can shield it by some bio inspired strategies. So, you can shield it first of all by coating with lipids. So, this is something that has been inspired bio cell membrane itself, all cell membranes are coated with lipids. So, you can coat with lipids, which are biocompatible as well as something that the body consider itself, that will increased circulation time.

Obviously polymers we have extensively talked about like PEG. So, you can coat it and that connects as a windshield wiper as a shielding effect; you can coat with carbohydrates for that matter. So, carbohydrates like your hydrophilic polymers are also very hydrophilic and in fact, carbohydrates are polymers long chain carbohydrates. Some of the natural polymers, which actually the cell itself has. So, if you look at cell. So, if I say this is a cell; the cell has heavily glycosylated proteins that are present and they also act as a windshield wiper and not let any nonspecific interaction to happen.

And then you can also coat with some proteins to mimic the body as I said most of our cells have proteins on their surfaces. So, you can also use that to put on your particles

and have some bio shielding applications shielding it from any of the immune system many of the degradative environment that is present in the surrounding ok.

So, we will stop here and getting this forward in the next class.

Thank you.