Drug Delivery Principles and Engineering
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Lecture - 14
Hydrogels – I

Hello everyone, welcome to another lecture for Drug Delivery Engineering and Principles., just a quick recap of what we have done in the last class. So, in the last class we continued our discussion with non erodible matrix system these are matrix systems that can be used to essentially release out any kind of drug that you want to deliver to the system, via mainly basis of diffusion or through some sort of solvent base extraction of these molecules.

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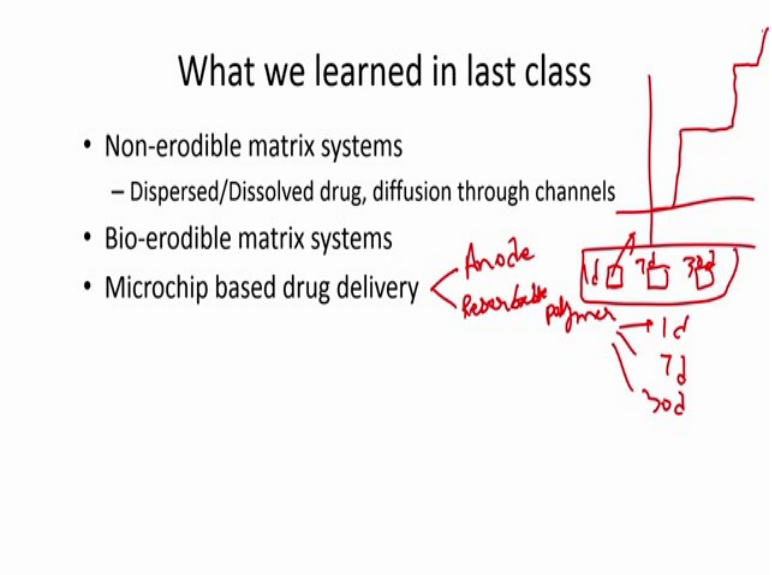

And so in this we discussed there are four cases and then in this last class we discussed the last two cases. So, essentially in a non erodible systems, you can have systems where the drug is either dissolved or dispersed and then the other scenario is, the drug just diffuse out throughout the matrix or it diffuses through the channels.

So, we discussed the first two first which was the drug is either dispersed or is dissolved, but it is coming out through the entire system and then in that last class we talked about in the case where the drug is coming out through the channels. As its really nothing much different here, but the porosity and the tortuosity of these channels gets accounted

for. Then we talked about the bio erodible matrix systems these are very similar to non erodible matrix system these are systems which have encapsulated the drug into their volume, but in this case they are now bio erodible; that means, that the when they are put in media which is biologically relevant they can erode.

So, they can either degrade by surface or bulk some things that we again discuss in the past. Then towards the end we talked about microchip based delivery, so this in this case we discussed two cases, one was anode based in which you have a reservoir that is capped with some thin metal anode films and then once the current is applied these things degrade and whatever is in the reservoir gets dispensed into the system.

And then the other thing we discussed about was instead of having in this anode based we can have it as a resorbable polymer and then this case became predefined as to this will degrade let us say in either 1 day, 7 days or 30 days and then depending on if this is 1 day, this is 7 days, this is 30 days, then you will get that release which will look something like.

So, at first it will be 0, at day 1 it will suddenly burst release out once this membrane degrades, then again it will be 0 then it will release out again and then same thing again depending on how much you have and what time points you are looking at.

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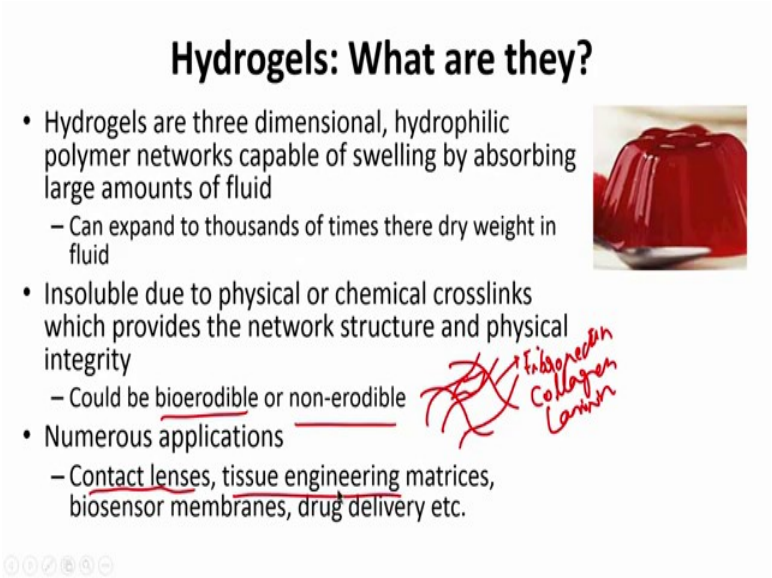

So, today we are going to talk about another very important class of drug delivery vehicles and these are called hydrogels. So, hydrogels are very widely used in the literature there a big in fashion at this point of time currently for the last 5 years and they have lots and lots of attractive properties which makes them very usable currently I am going to talk about some of these.

So, if I strictly define hydrogels these are essentially nothing, but the three dimensional structures, anything that has some sort of a length, breadth and height can be considered as three dimensional and so like all the other bio erodible matrixes that we also talked about, are all three dimensional and they are made up from a very hydrophilic polymer networks.

So, these hydrophilic polymers can be a variety of kinds, can be a variety of groups involved in there, but the essential thing is they are very hydrophilic and so because they are so hydrophilic they tend to absorb water and because of that if you make a matrix out of these hydrophilic polymers, it will absorb water and starts to swell.

So, here is an example here, where you can see that it is a jelly that some of you may have eaten during your course of life and this is essentially nothing, but if you have ever touched jelly it is a very squishy, very soft material, but again can have lots and lots of water compared to the actual polymeric content that might be present in a system like that.

So, as I said, they can swell, it depends on what polymers and what sort of cross linking is being done to maintain this polymer in a structure, but then they can expand to even thousand times there dry weight in fluid. So, you can have a dry hydrogel, but when it comes in contact with the aqueous fluid, it can absorb lots and lots of water and starts to swell and that swelling can be even up to thousand times.

They are of course, insoluble any kind of gel or any kind of device that we are talking about these are all insoluble because they are physically or chemically cross linked and that is how they provide the network structure. So, if it is soluble; that means, that individual components will continue to break apart and then start to just kind of roam around as soon as the solvent is put but if they are insoluble of course, that means, that they will remain as intact as they were initially.

Of course, like all the matrix systems we talked about earlier this is also one sort of a matrix system these could be bio erodible or non erodible; that means, that over a period of time it is bio erodible and then essentially; that means, that the hydrogel will degrade over time.

And then if it is non erodible; that means, that we will maintain structure it would not really have any loss of the polymer itself the drug may or may not come out that depends on the system what you are designing, but the biological fluid will not cause any kind of erosion to happen. And there are several and several applications to this, they have been used in contact lenses.

So, the contact lenses you will see people wear on their eyes in the front not only they have power, but they can also protect the eyes and again hydrogels are the one that I used very often to make that, they have used very widely in tissue engineering matrices and we are going to talk about that as we go along in the course, they have been using biosensors, they have been used in drug delivery. And I think one of the thing that really makes them so attractive is the fact that, if you look at our own body and whatever we have is, we basically have cells and proteins and different kinds of other bio molecules in our body, but then the cells typically we will find are embedded in some sort of a 3D structure.

So, if you look at cells, they just do not sit ideal in the layer, but there is some sort of a 3D matrix like, that it could be some kind of a ECM component like fibronectin or collagen or laminin and there are few others, but then what you will find is the cells are always sort of sticking to some sort of a structure if they are stagnant or unless they are flowing in the blood then it is a different case, but most cells you will find in the body are stabilized in some sort of a structure like that.

So, because of that the hydrogels can act as a mimic to this ECM structure that I have drawn here and that can support both the cell adhesion, the cell migration as well as releasing different molecules. So, that is why they are very widely used for tissue engineering and again as I said as we go along we are going to give some examples and talk more about this.

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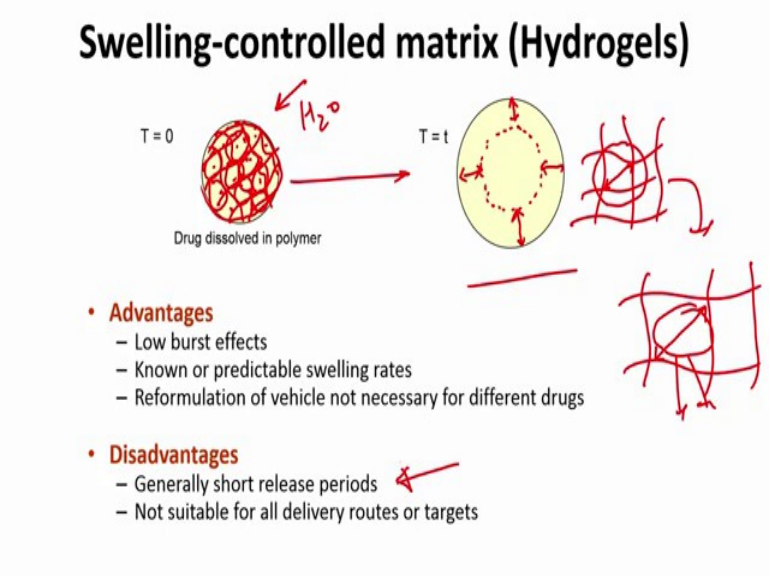

So, in terms of the drug delivery itself how does this work? So, you have a drug that is dissolved into the polymer. So, in this case the drug could be lying, again like the erodible and non erodible systems, the drug is trapped among these polymer chains that may be present in this hydrogel and the drug itself is fairly big that it cannot come out of these pores in these networks or even if it does it might be very slow, but once you put this in a solvent as we said that the hydrogels are capable of swelling, its going to start absorbing more and more water into the system and as it does that it will swell. So, maybe the initial shape was like this.

But now what has happened it has swelled in all directions and so because of this swelling, what will happen, these gaps would be in the polymer chains is going to increase. So, let us say if this was the gap here, as its absorbing more water these chains are getting stretched and stretched and what will happen is eventually it is going to turn into a structure like this where now, as you can see this gap is much larger than the gap here.

So that is how basically the drug will come out because now it can easily diffuse out, so let us say the drug was just big enough to entrap here, in this case the drug is small enough now or and the pores are big enough now that this drug can come out through these pores.

So, advantages are, it has low burst effects and the reason for that is drug is basically entrap it is not moving around. So, remember why was the burst effect present? It was present because drug would typically come out and sit right on the edges. So, if there is no movement of the drug because it is very entrapped in there it would not really come out and you would not get a burst effect. We can derive the equations as to how much its going to get enlarged, how much these pore sizes are going to become larger as it absorbs more and more water.

So, you can have some known and predictable swelling rates. So, that way then you can use mathematical equations to determine what sort of kinetics we are going to get for the release of the drug. And again the vehicle is fairly well controlled in terms of what is the pore size for different types of polymers and different types of concentration.

So, even if you change the drug from one to the other, its not like you have to now reformulate everything and basically right start from the stretch, what you can do is you can just replace the drug from whatever drug you were earlier using and if you know the size of the drug you can very well know the sort of a release rate and what sort of polymers to use to make this hydrogel.

What are some of the disadvantages? Generally, it is a very short release period we are talking about because once this is swelled and the drug can very rapidly come out on the basis of diffusion and that kinds of limits as to how long you can release drugs from them, but again there are few strategies to counter that and we are going to talk about that.

And again it is not really suitable for all delivery routes or targets now you have to worry about your actual implant changing in size. I mean let us say I have a 1 millimeter implant and I want to implant it let us say in my eye, but if I know that 1 millimeter is going to become 10 millimeter I do not want that implant to start pressing on different tissues of my eyes and causing damage, same with the blood vessels right.

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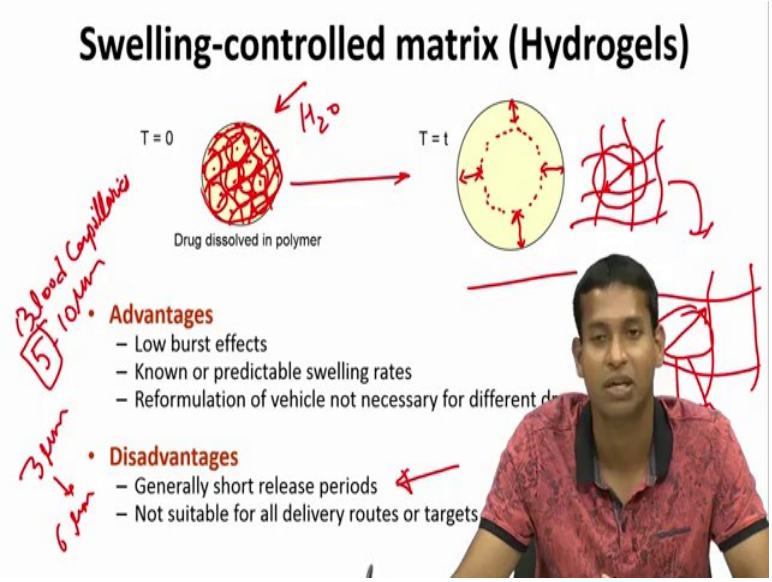

I mean we know our blood vessels the minimum of them the smaller capillaries at about 5 to 10 microns, the blood capillaries and so let us say if I have hydrogel particle which is let us say 3 micron. So, it is fine to inject that because its lesser than that, but if I know that this 3 micron is going to then increase and become let us say 6 micron, then I cannot inject into the blood right because you have inject it into the blood what will happen these 5 microns, 6 microns capillaries will get clogged. And not only that, but their downstream tissues where these capillaries were supplying, those cells will now would not get oxygen, would not get nutrients and they may start to die, this may cause heart attack or this may cause strokes, if it if those capillaries are involved in brain, so and this is a big issue there.

So, again as I said its not really suitable for all delivery routes and targets, but then again the good thing is we know what final product we will get, so we can choose where to inject it. So, let us say if I want to put it in under the skin and I am if the skin bulges a little bit and then I can use this.

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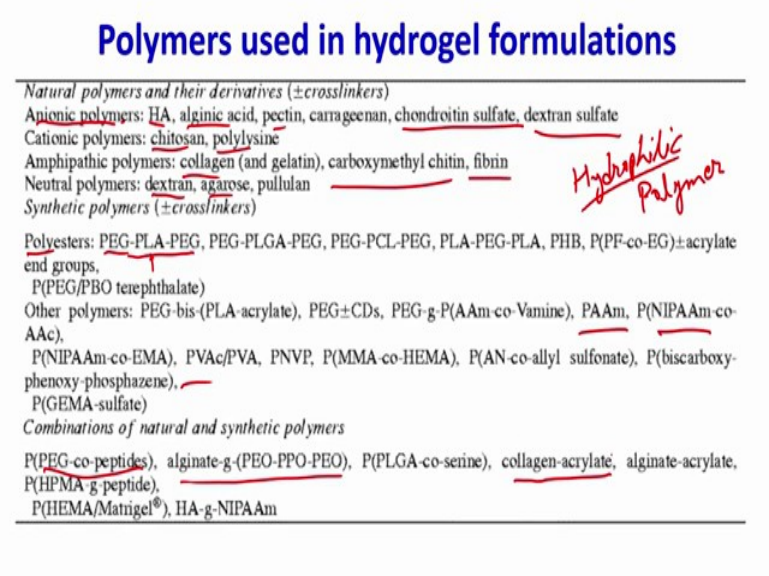

So, some of the polymers that are used in hydrogel formulations, so again as we discussed this can be natural polymers or this can be synthetic polymers. And of course, when I say polymers, we also talk about cross linkers these are small molecules or big molecules that are involved in cross linking these polymers to form a mesh like network and but right now we are mainly talk about the polymers themselves.

So, they could be anionic polymers for natural, so HA very commonly found in our joints, alginic acid, pectin, chondroitin sulfate again something found in the joints the sugar moieties like dextran sulfate. You can have cationic polymers such as chitosan and poly lysine. So, these are again very well characterized and found throughout the body.

Then you can have an amphipathic polymers like collagen, so these are not really charged, they have both charges and essentially the charges are balancing themselves out you can have fibrin, you can have CMC or it can be natural polymers these could be dextran, neutral polymers, these could be dextrans, these could be agarose and other molecules. Again remember all of these molecules need to be hydrophilic right as I said the hydrogel will only form with the hydrophilic polymers.

So, again all of these can also form various other kinds of things along with some other polymers too, but if it has to be hydrogel it has to be hydrophilic. And then let us talk about some synthetic polymers, so polyesters again PEG is a very hydrophilic polymer and again very widely used for making hydrogels. So, in this case it even list as

combined with the PLA which is not as hydrophilic, but then the whole combination of this product is fairly hydrophilic.

So, you can combine PEG with different kinds of polymers, you can have some other polymers such as polyacrylic acid and Poly NIPAAm, PVC, so all of these are again used quite often. And then you do not really have to have categorically different that it has to be either natural or synthetic you can have something you can combine the two.

So, you can combine PEG with other peptides to form a polymer, you can combine alginate with other PPO type polymers to make them, you can have collagen and combine it with some sort of an acrylic polymer. So, all of this is again widely used in the literature.

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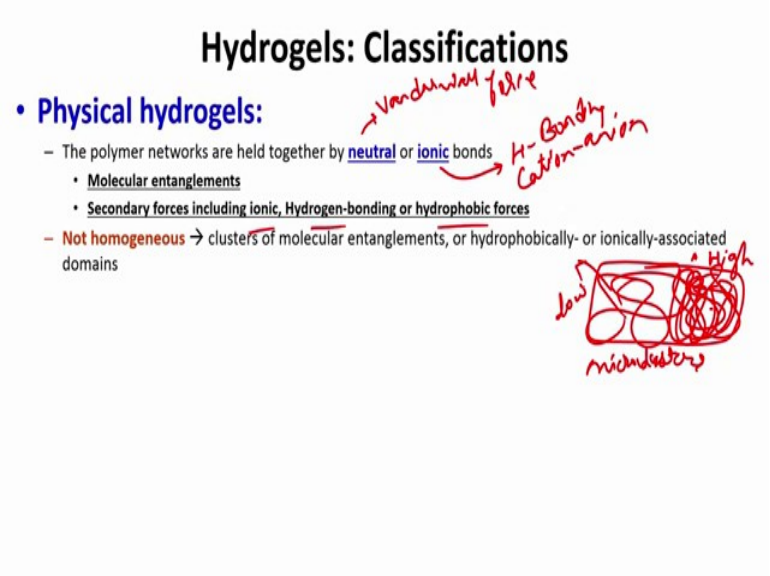

So, how do we classify hydrogels? So, there are various ways you can classify hydrogel one is on the basis of first of all how they are forming their structure. So, this could be either a physical hydrogel or and this could be a chemical hydrogel. So, let us talk about physical hydrogel first. So, these again are polymer networks that are held together by neutral or ionic bonds. So, when I say neutral bonds I am talking about Van der Waal forces right.

So, this could be Van der Waal forces and ionic would be either H bonding or it just could be interaction of cation and anion. So, these are essentially nothing, but these are

molecular entanglements. So, you can consider it as if you have very long chains of these polymers and they just cross each of the several times. So, I am sure if you guys have using earphones, you have seen sometimes it gets entangled and form this knot like structure.

So, if you have enough of your headphone leads which are very long and you will essentially end up with some sort of a giant mesh of a network that will be molecularly entangled with each other to form sort of a 3D structure. So, that 3D structure is now made about hydrophilic polymers and happens at a much smaller scale then we are talking about a hydrogel.

So, as I just said there are some ionic hydrogen bonding in hydrophobic forces involved essentially Van der Waal forces, they are typically non homogeneous as I said they are this random entanglement of chains. So, it is not like they are very well ordered or structured, so at some parts of a hydrogel, so, let us say if this is my hydrogel at some part of the hydrogel what you can have, you can have quite a bit of chain coiled around to form a gel and in the other parts you can have very sparse chain forming around.

So, they can be micro clusters like this, where it could be high molecular entanglement versus low molecular entanglement. So, in this case low and high and so if you start comparing between the two, you can find that the drug release from this area will be much slower just because the cross links are quite a bit and the drug cannot diffuse out very easily, while the drug from this is fast compared to the overall structure. So, they tend to be non homogeneous.

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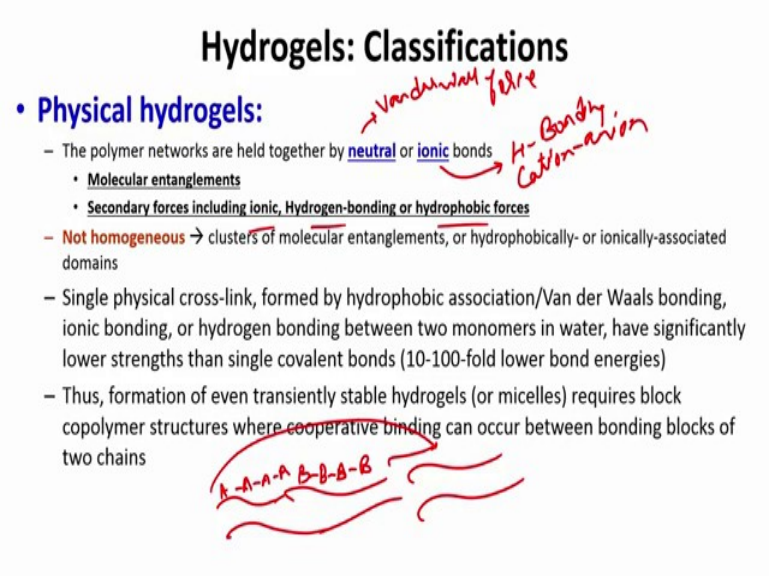

So, let me just delete this. As I said there are physical cross link these are formed by hydrophobic association, Van der Waal bonding, ionic bonding, hydrogen bonding between two monomers in water they have significantly lower strengths. So, covalent bonds are typically much higher strength than these physical interactions. The strength for these physical interactions lie in the numbers. So, you have a one covalent bond whereas, for each one covalent bond for these physical interactions they might be almost hundreds and thousands of a small interactions happening here. So, just to keep in mind that, there individual bond strengths are fairly low whereas, in covalent bonds it is fairly high.

So, thus formulation of even transiently stable hydrogels require block copolymer structures where cooperative binding can occur. So, what essentially this means is let us say if I have a block copolymer with let us say monomer A here and B here.

So, if I have these and then there could be multiple chains of these right its easier for them to then come together and because there are let us say A can roll around and interact with the B here there lots of interactions here, they typically tend to form a better physical hydrogels than the individual units and that is how these ones will be much stable.

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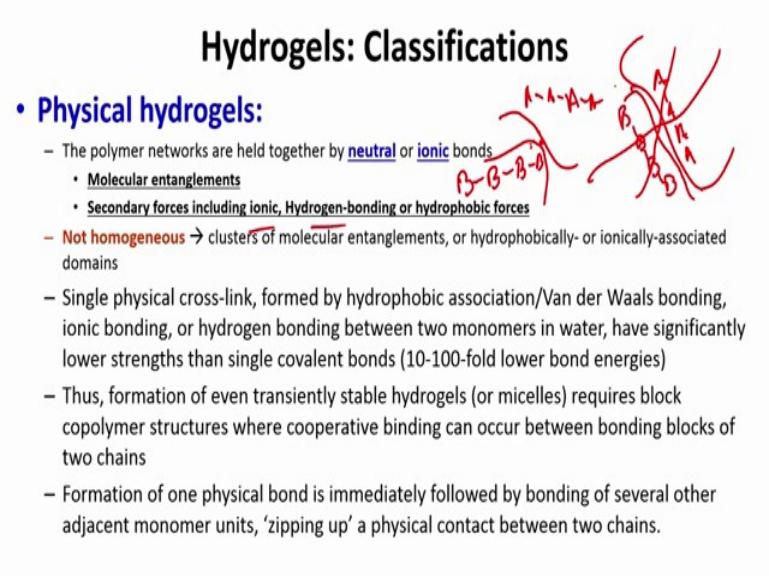

And then formation of one physical bond is immediately followed by bonding of several others. So, at the time you are basically talking about zipping up these contacts. So, you can have; you can have one bond forming between these two, let us say this is A A A from one chain and this is B B B from another chain and as soon as they come in contact and start interacting, now these surrounding chain surrounding atoms are also in close together. So, they will start two kind of zip this through. So, very soon you might have something like this forming where now you have A,A,A from one chain interacting with the B domain of the other copolymer.

So, that is how their structure goes and again you can assume that there are thousands and millions of these scenes and they will cross each other as well and make this a very stable structure.

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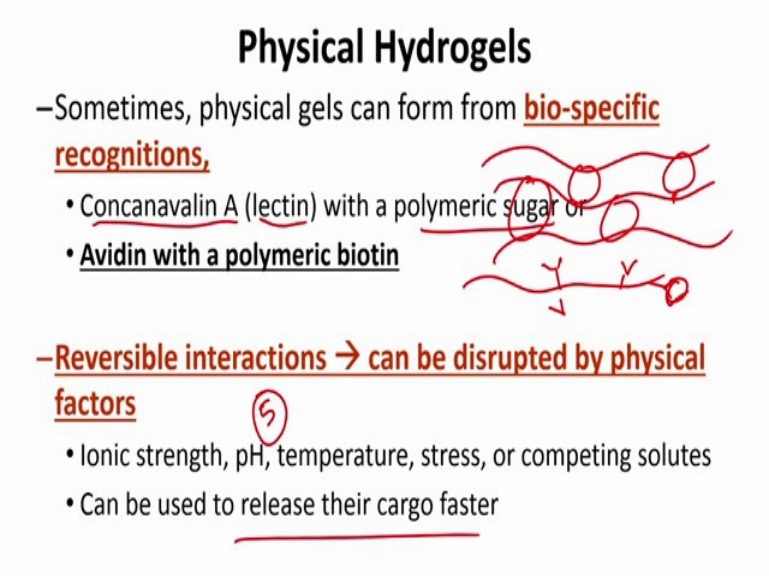

So, something more on the physical hydrogels, sometimes physical gels can form by a bio specific recognitions. So, it may not be a covalent bond and it would not be any of these interactions, but then we know in biology there are lots and lots of specific interactions. So, you have a concanavalin A, which is a lectin; lectin are essentially proteins bind into the sugar. And so again this has a natural affinity to bind sugar. So, if you mix this lectin with this polymeric sugar what will happen is let us say if this my polymeric sugar which is large unless that this protein is fairly small. Once this protein binds to this chain on one side it will tend to bind to another chain and then you can have several of these proteins at several locations kind of acting as a cross linker and that essentially causes the bond to form.

Another good example is avidin with the polymeric biotin, so avidin again has a very high affinity for biotin one of the strongest affinity pairs out in the system in biology. So, again the same thing goes here let us say you have a polymer chain that is conjugated to avidin and now if you come and put biotin in this system. So, what will biotin do? The biotin will bind this as well as take another avidin from another place and bind to another chain. So, that is also kind of acts as a cross linker for avidin modified polymers. So, both of these are fairly feasible and again there are several systems out there this is just two examples I am giving you right now, but something like that can progress to hydrogels.

And then these are again there were several interactions these can be disrupted by some physical factors as well. So, let us say this interaction maybe is not stable at a low pH maybe this evident gets denatured or the lectin gets denatured or maybe the temperature is too high and the molecular movement masks the energy because again as I said these are very small bond forces that we are talking about. So, these can be then disrupted.

So, so something like ionic strength is one if there is an essentially ion-ion interaction happening between cation and anion if they increase and ionic strength what will happen? The dielectric constant will increase and so the by the Coulomb's law the dielectric constant is at the denominator. So, what will happen is the attraction force will decrease and that may be sufficient to kind of disrupt this physical hydrogel and so all of these can be used as a trigger to actually release the cargo faster right.

So, let us say if I want a system that only releases things at a pH of let us say 5 and I know that maybe the two polymers that I am using to form these hydrogels stop interacting with each other at pH of 5. So, what will happen is at a pH of 7 they are interacting well and it will remain as a structural particle or a structural gel, but once let us the cell takes it up and brings the environment locally down to pH of 5, then they will just break apart and release whatever was present in the system .

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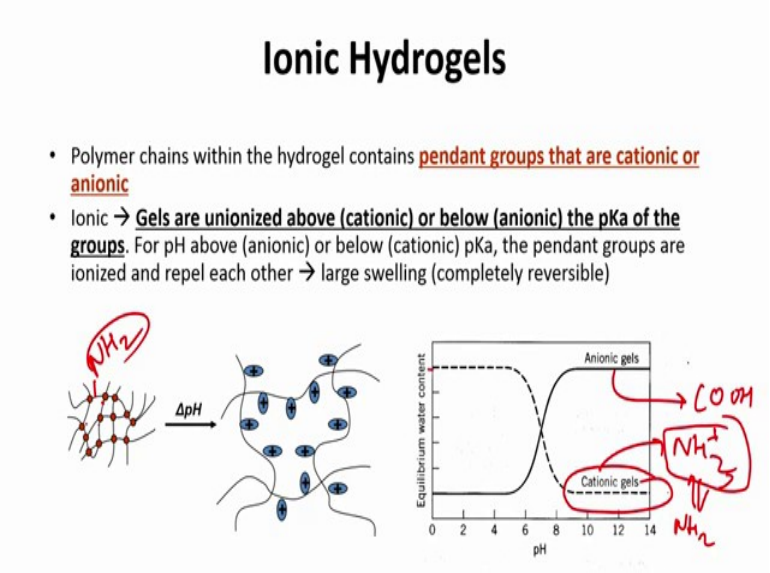

So, another class of a physical hydrogel is ionic hydrogels. So, these again like the physical hydrogel we talked about these are polymer chains that contain cationic or anionic groups. So, essentially this is just one special case for your ionic hydrogel.

So, these gels are typically an ionized because there are equal amount of cationic-anionic chains have come together and of course, as I said, if you change the pH the molecules that are making a cationic or anionic may change and that may itself cause either the gel to just fall apart or may cause a differential in swelling which could be completely reversible.

So, an example here let us say these chains were initially all bonded together and they are very stable, but along with these cross linking places there is a functional group let us say carboxyl, which or let us say amine let us say amine in this case.

So, at a pH of 7 we know that this amine is going to be typically; that means, will have a pKa which is much higher than 7. So, they may be charged and then once the pH has now dropped a little bit, if the charges may change and because of that since there are lots of amines and they will start repelling each other if they are charged, they are similarly charged and then these cross linked distance will increase. So, you can have a system, so, let us say if you have a cationic gel, then that cationic gel will be uncharged because all the positively charged will not be present on amines.

But then and let us say the cationic gel here let us say for an example is an amine and then anionic gel for an example is a carboxyl. So, let us say at certain pH let us say 8, these amines are positively charged below that pH and as the pH increases this amine basically undergoes transformation to a neutral molecule.

So, because of that, now they do not tend to repel each other they may have a certain amount of stretching present, but as you change the pH this stretching may further increase because now not only there is absorption of water, but there is also an electrostatic force that is repelling each of these chains.

So, you see that now this swelling has increased quite a bit, vice versa for anionic gels and now you are essentially talking about changing the pore size, which will cause the change in the release rate of whatever drug is encapsulated. So, we will stop here, we

will continue our discussion with anionic gels and further the physical and chemical crosslinked hydrogels in the next class.

Thank you.