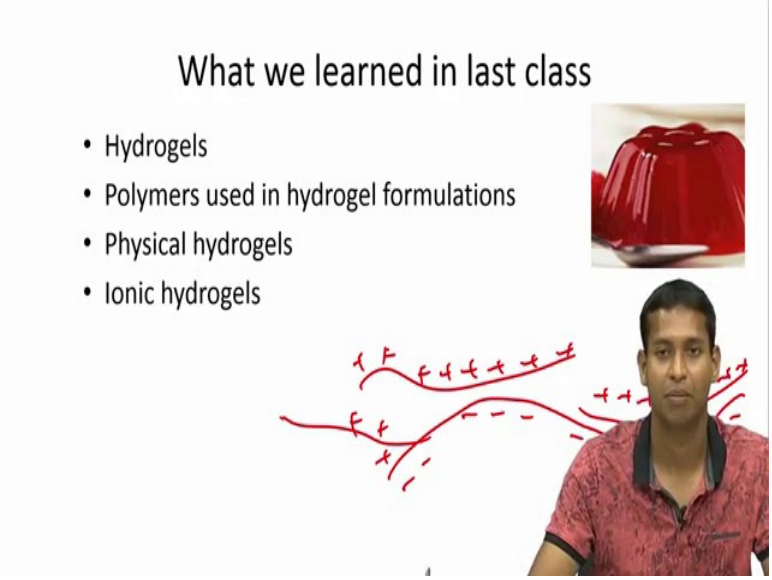
Drug Delivery Principles and Engineering
Prof. Rachit Agarwal
Department of BioSystems Science and Engineering
Indian Institute of Science, Bengaluru

Lecture - 15
Hydrogels – II

Hello everyone, welcome to another lecture of Drug Delivery Engineering in Principles.

(Refer Slide Time: 00:33)



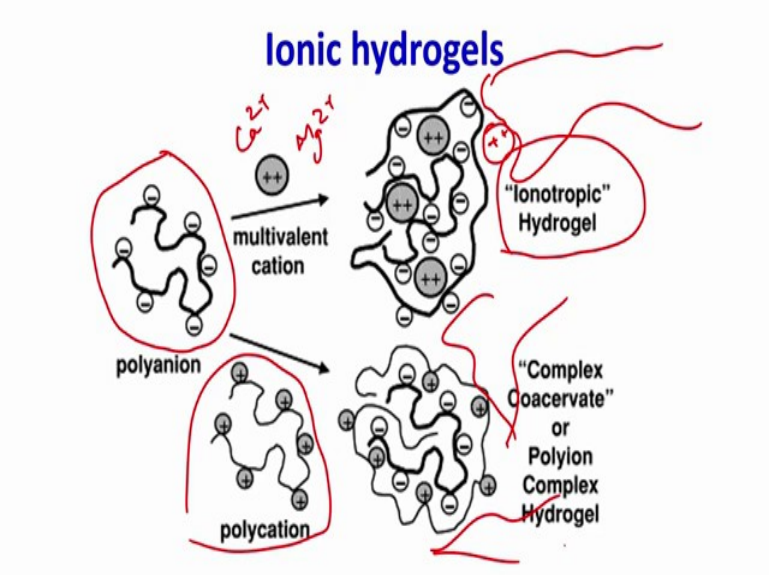
Let us do a quick recap of what we learned. We are now discussing Hydrogels. So, we introduced the hydrogels in the last class; it is a big topic. Hydrogels as depicted here, like a jelly, these are gels at a made up of very hydrophilic polymers and they can absorb a lot of water. So, we talked about hydrogels in general, we talked about polymers that are used in hydrogels. So, there are all types of polymers, both synthetic as well as the natural, if they are natural they are essentially meaning that, they derived from something and that is found in body; these can be sugars from the body like dextran, chitosan.

These could be other kinds of proteins like collagen, fibronectin and some other body drived source; eyebrows and or there is synthetic; these are PEG based or PVC, poly NIPAAm based polymers that are very widely used. Then we talked about physical hydrogels; what are physical hydrogels? Physical hydrogels is nothing, but these are gels which are formed by molecular entanglements of long chains; they may have some sort of Van der Waal interaction between them or some ionic interactions, some other

interaction may also be present, they may have affinity, if their biomolecules and things like that. And so, they essentially form these entanglements and results in a hydrogel formation. And then, as a special case we were talking about ionic hydrogels. So, these are again hydrogels, that are interacting with each other using ions.

So, you can have two types of chains; one can be positively charged and another chain could be negatively charged and they will interact with several other chains, there also. So, essentially these kind of a big giant mesh is formed that results in a polymer gel being formed, which is again if these are hydrophilic polymers, then they will also have a very high absorption of water resulting a hydrogel formation.

(Refer Slide Time: 02:44)



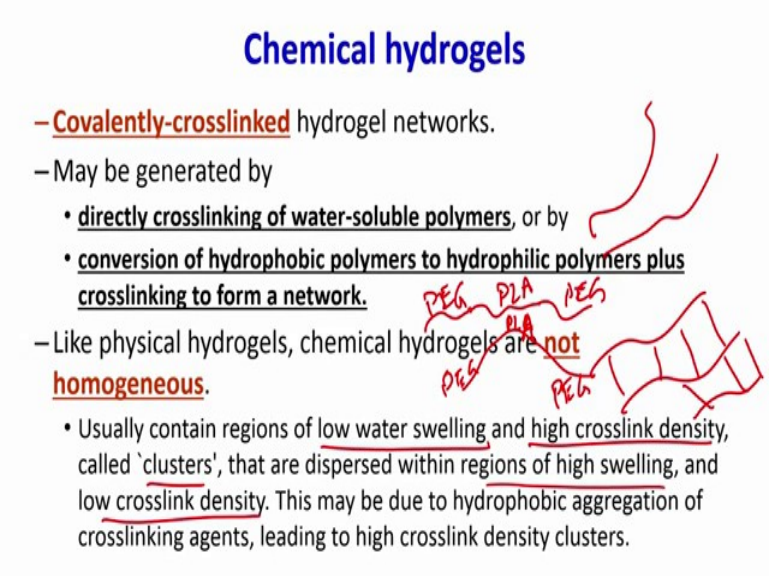
So, a little bit more in the ionic gel. So, here we are talking about, let us say, we have a polyanion containing lots and lots of negative charges on that; if you put a multivalent cation, you do not even have to put; let us say, another chain containing that.

Let us say, if you put a multivalent cation, could be calcium, could be magnesium; what will happen? That, these individual atoms of calcium and magnesium will interact with multiple or at least two of those negative ions and they will result in a formation of something called as an ionotropic hydrogel and so, again there will be another calcium molecule here, that will have interaction with another big chain. And so, that is how you can imagine the whole network growing and making up very complex structure having lots of interaction between single chain with several other molecules.

And the other case could be you can come up with a poly cation, that also contain instead of just two or three that may also contain positive charges throughout the structure like the polyanion and then, you can have something which is a poly complex coacervate or a polyion complex hydrogel.

So, depending on what ratios are mixing them, they can either just precipitate out or they can form a gel while interacting with several other chains. So, that will essentially result in a large network being formed; just like the first case.

(Refer Slide Time: 04:14)



So, let us talk about chemical hydrogel. So, unlike the physical hydrogels, these are covalently linked hydrogel networks. So, essentially whatever bonds are there they are actually covalently linked with each other and these covalent bond could be again of several types; we have discussed few in the poly meter conjugate. So, this could be an EDC coupled reaction, this could be a maleimide reaction, some click chemistry.

So, all of those are very feasible here, any kind of chemical bond that is being formed. So, these could be generated by directly cross linking of the water soluble polymers. So, you can have polymers and that have several functional groups on them, when they are water soluble and you can directly cross linked them or you can have conversion of some hydrophobic polymers to hydrophilic polymers and then cross linking.

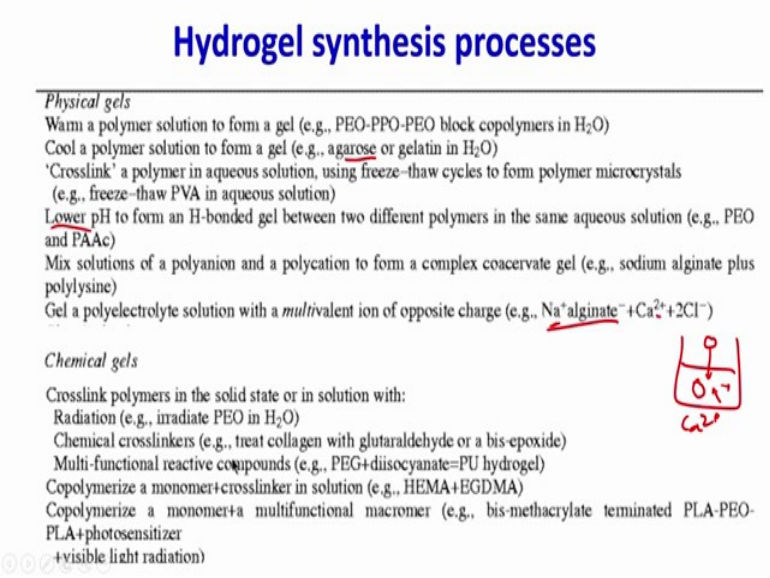
So, let us say, example I gave you in the last class was PEG PLA PEG, where PLA was a hydrophobic polymers. So, what I have done is I am taking a hydrophilic polymer; I have conjugated it to PEG and now, the overall this particular chain is fairly hydrophilic and then, I can have the cross linking happen between different chains to form a hydrogel physically cross linked gel.

So, like physical hydrogels chemical hydrogels are not homogeneous, they are somewhat more homogeneous, than the physical hydrogels, but even then, you can imagine let us say, if I had these long polymer chains and I have these cross linkers, that are being used to cross link them, depending on the local concentration the cross linker; you may have certain micro domains, which are heavily cross linked whereas, the other portions may not be as cross linked. So, there might still be non-homogeneity, that is present into the system. And so, if I have let us say a heavily cross linked area, then it will have a low water swelling and high cross link density and so, this can be called as clusters.

So, this will be dispersed throughout the regions, which may have a high swelling because of the low cross linking density and this could be because of again, as I said several regions you can have hydrophobic interactions that are also presence, if you know PLA this may want to interact with another PLA of a different chain whereas, the PEG may try to separate it out. And so, they might be competing force that may cause the aggregation of PLA domains and causing a very high density of the polymer at a certain region. And so, these things can occur because of that or they might be just because, when the gel was forming there were some diffusion limitations of the cross linker and that, caused a certain region to be highly cross linked than the other.

So, all of these are very feasible, but again and they are not very homogeneous, but they are more homogeneous then let us say a physical hydrogel.

(Refer Slide Time: 07:12)



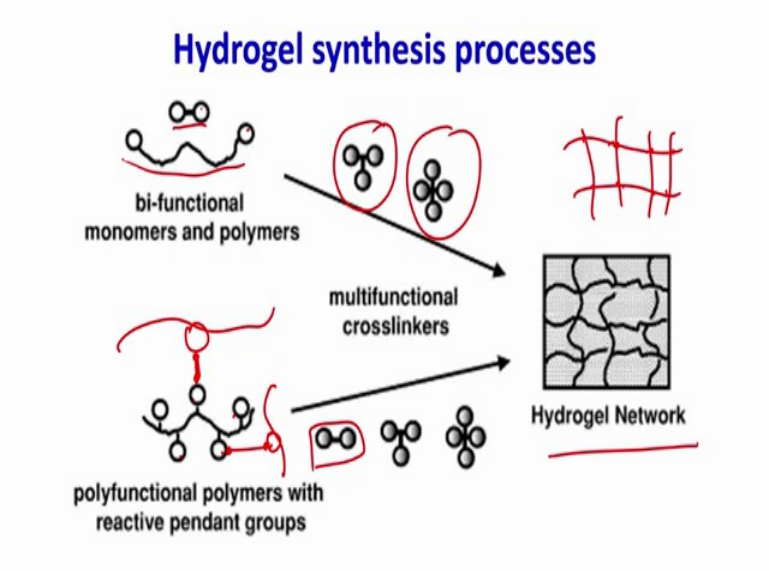
So, hydrogels synthesis process, again this is a typical example not all hydrogels are going to be formed via this method, but you can have a physical gel; you can warm a polymer solution to form a gel. So, let us say you warm it up and then slowly cool it down and what will happen is, now these chains have lots of time to interact with each other because, you increase the temperature that diffusing very fast and they may find their pairs they want to interact with and then, when you slowly cool the temperature down what will happen is; they may start to form these physical gels essentially interact with each other with Van der Waal forces, hydrogel bonding, ionic interactions all they all that may start happening.

So, cool the polymer to form a gel. So, something like agarose is very widely used if you guys have ever worked in a lab, you may have run DNA gels and very easy way to do that is to just mix some agarose in water heat it up to make it solubilized and then, as you cool it down these forms these gel like structure, that you would then run your DNA to resolve to see, what sizes of DNA you have got. So, that is just one example you can lower the pH. So that is another way you can form these. So, again as I said maybe some gels are most stable at a lower pH. So, you lower the pH that may increase the interaction, that may change the charge. So that, may result in the formation of these gels you can mix a poly cation and anion at a certain ratio to get a gel.

So that is another possibility, that you can use. So, another one with that its very widely used is the alginate gels. So, what is done is sodium alginate, which does not form cross linked, because this is only a monovalent cation, but then, if you dropped into a solution containing calcium then, what will happen? Let us say, if I have a beaker, that contains calcium 2+ and if I make a drop of the sodium alginate and let it drop in calcium; what will happen? The sodium will leave the system and calcium will go in; because, it has higher affinity it has to 2+ positive charge and so, what will happen? Is this drop will immediately polymerize to form a hydrogel of alginate.

So that is another way you can form these physical gels and then, in regards to chemical gels; its fairly straightforward you can have some sort of a cross linker, that is present that kind of diffuses through the chains and then, cross linked different sections of the chain; you may have some sort of a radiation, that is happening. So, maybe it is a UV based polymerization in presence of UV, which generates radicals, which then forms these polymers and then and causes these polymers to form hydrogel. So, all of these can happen, you can mix different kinds of copolymers together and they may just have functional groups, that are reactive against each other and then, form bonds. So, all of that is fairly feasible.

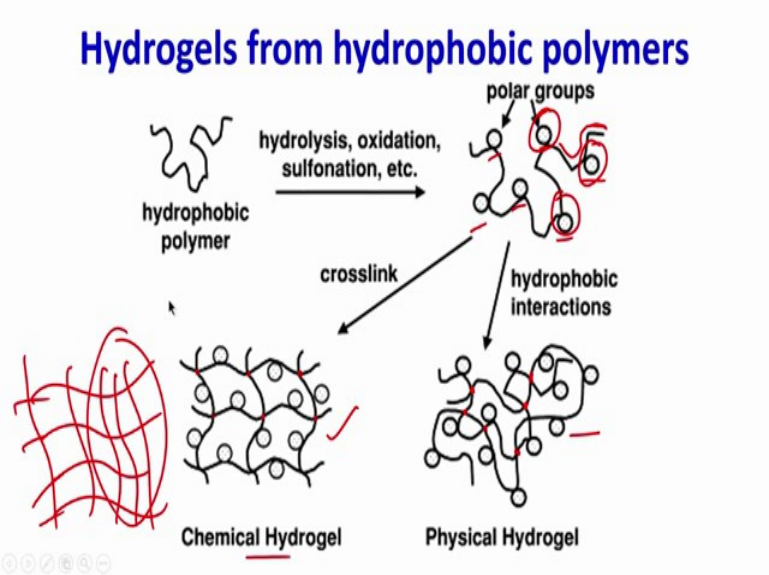
(Refer Slide Time: 10:11)



So, here are some further examples. So, you can have a bi-functional monomers in polymers. So, it could be either a monomer or it could be a polymer and then, you mix it

with some multifunctional cross linkers and what will happen? Is these will go and bind to different areas and essentially, you will have cross linking happening at all these places to form a mesh like structure, essentially giving rise to a hydrogel network. Or you can have just a big chain containing several and several of these reactive places and then, all you do is just mix your multifunctional cross linkers and they will then, cross link with another chain like it shown here and then, this may be linked to another chain. So, that is how the structure can propagate and essentially form a hydrogel network.

(Refer Slide Time: 11:12)

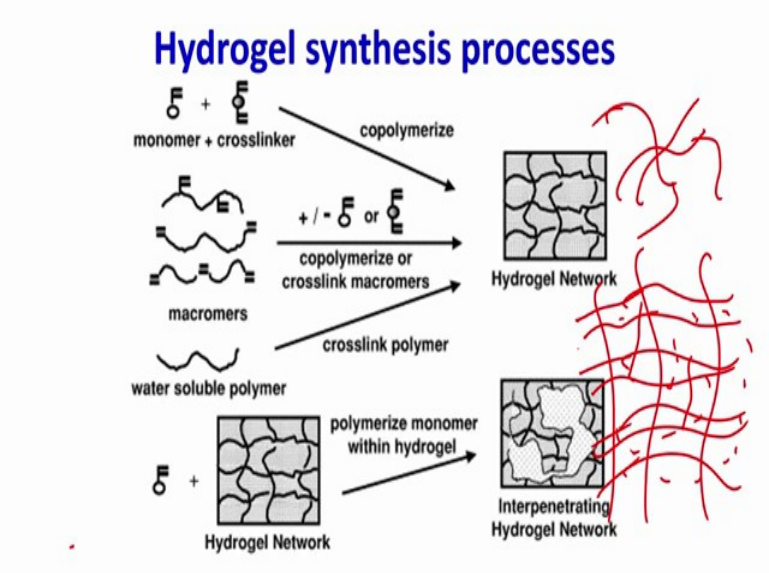


So, when we talk about hydrogels from hydrophobic polymers, again as I said by definition the hydrogels are made from very hydrophilic polymers. So, you have to somehow make them hydrophilic. So, you can take a hydrophobic polymer; you can modify its backbone to add lots and lots of polar groups. So, what will that result in, that will result in some sort of an amphiphilic polymer because, you have all these domains, which are fairly hydrophobic whereas, these domains, which are hydrophilic. And so, these domains can then interact with each other, the hydrophobic domains at several places to form a physical hydrogel or you can then, use these polar groups or some other functional group two kind of cross linked them at several places using an actual chemical bond and that will result in a chemical hydrogel.

So, as you can see from here also this looks a lot more homogeneous than this does but, again this will also have some micro domains, it will not be as well organized as is

shown here because, you may have some domains where, you have very close chains and then, you can have some domains where the cross linking may not be as close as the domain showed here.

(Refer Slide Time: 12:36)

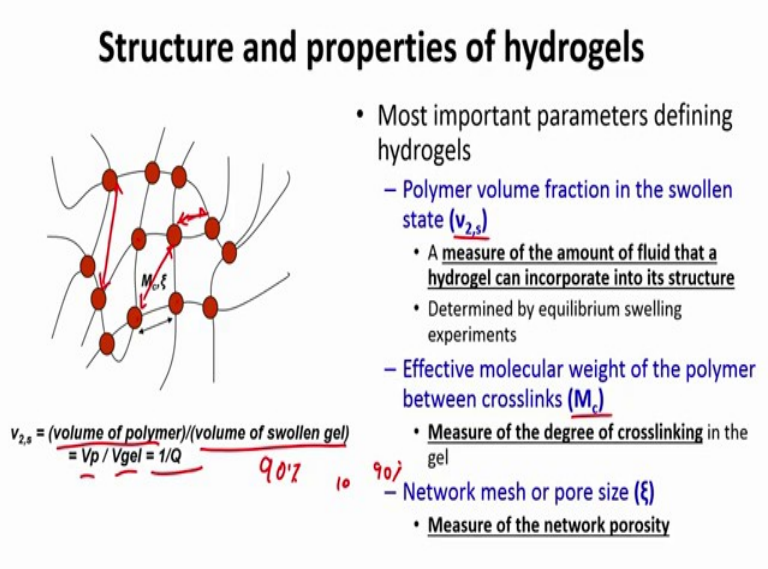


So, more on the hydrogel synthesis process; so, again you can take monomer and cross linkers and copolymerize them. You can have macromers and then, you can use a cross linker just in the way I described in the previous case or you can have some other format. What you can also do is you can form a hydrogel. Let us say, I form the hydrogel and now, what I do is, I then add some other different copolymer or some other different monomers into that which then diffuses throughout this network, which is small enough to go into these pores of these and then, I add another cross linker.

So, let us say, if I am basically having another different chain; that comes with another cross linker and cross links it. So, basically now, what I am looking at? I am looking at a domain, where you have two hydrogels that are just interlinked with each other. So, the chains are crisscrossing through all these polymer networks and that is essentially causing them to cross with each other causing this curt of interpenetrating hydrogel network. So, you cannot separate out the 2D two gels, because the chains are actually physically entangled with each other. But then the two hydrogels have actually separate, you can have separately formed them together, but now, what you have done is from them in situ, together in a single system.

So, these are called interpenetrating hydrogel network. What are the advantages of such a system? These can have a very favorable properties; you can have, let us say one gel, which is structurally and mechanically much stronger than the other, but then, the other gel may be good for the cells. So, what will happen now? Because now you have formed them together into a system, it will also be mechanically good as well as the cells can still attach to it using the other hydrogel network. So, these are some of the advantages here.

(Refer Slide Time: 14:56)



So, what are the some of the structure and properties of the hydrogel? So, let us define some terms. So, these are some of the most important terms in defining hydrogel. So, one is polymer volume fraction In the swollen state. so, this is defined as v2s. this is essentially, just a measure of how much amount of fluid that, the hydrogel can incorporate into its structure. So, you can have a polymer, you know what is the volume of that polymer that, you started with.

Then, form this hydrogel and then, you see, what is the final volume of this hydrogel. So now, you can have some sort of estimate as to, what is the v2s is, as well as how much water it is absorbed?

$v_{2,s}$ = (volume of polymer)/(volume of swollen gel)

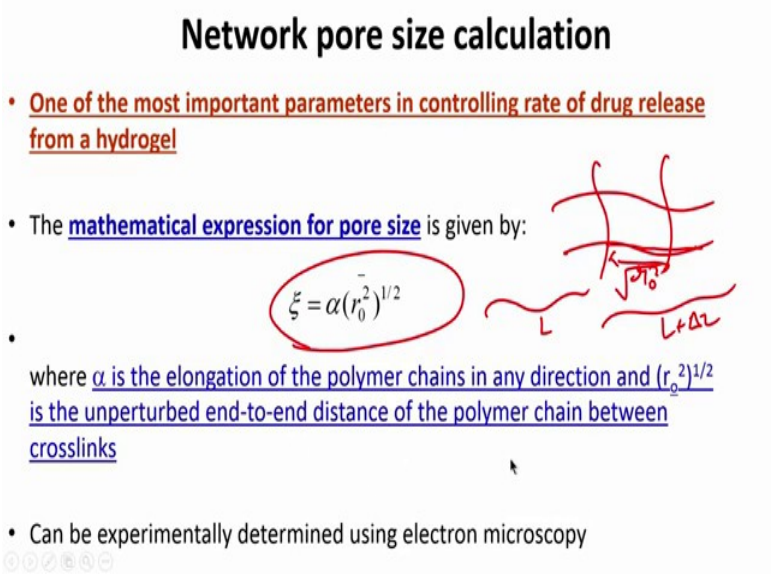
= Vp / Vgel = 1/Q

which is an estimate of how much the swelling has actually happened.

So, if these if this comes out to be, let say 90 percent then, only 10 percent is water there, where as this comes out only is 10 percent then, it is almost has swelled 10 times, compared to its original volume. Then you can have effective molecular weight of the polymer between cross links. So, let us say, this is the cross link and again, as I said it could be non homogeneous. So, some cross links might be fairly well apart and some might be very close together. So, this is an average effective cross linking of this and its defined as Mc and so, Mc is nothing, but the distance between the two cross links on an average; and then, you can have a network mesh or pore size.

So, very similar to the Mc, which is the effective cross linking is, essentially, what is the pore size? So, what diameter pore are we talking about? How can we define the distance between the different polymer chains? And so, this is a measure of what is the network porosity.

(Refer Slide Time: 16:58)



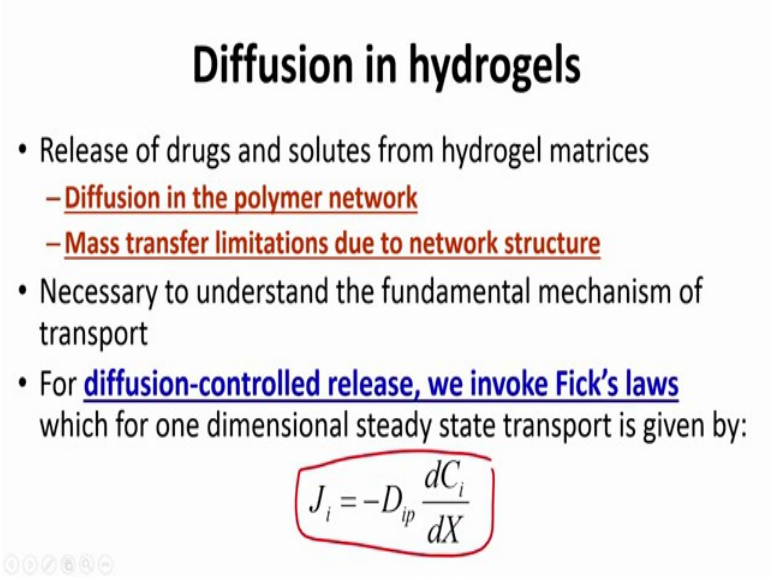
So, some network pore size calculation, one of the most important parameters in controlling the drug release rate is the pore size of this? The mathematical expression the pore size is given by nothing, but

$$\xi = \alpha(\bar{r_0^2})^{1/2}$$

and what that is is alpha is the elongation of the polymer chain. So, let us say, if my polymer chain is of a length L, after the formation and elongation it becomes L plus delta L. So now, we are talking about alpha is basically the elongation of this chain. Where, r naught is the unperturbed end to end distance between the polymer chain between cross links. So, let us say, if I make these cross links, this distance is r naught and to keep to make sure that, the signs are not changing in all. So, this is r naught square and root and essentially, this can then elongate as the swelling is happening and further increase and that, is how you can then define the pore size here.

So, one way you can do is, you can do some microscopy, could be electron microscopy, could be some other form of microscopy to sort of determine, what is the distance between these two units?

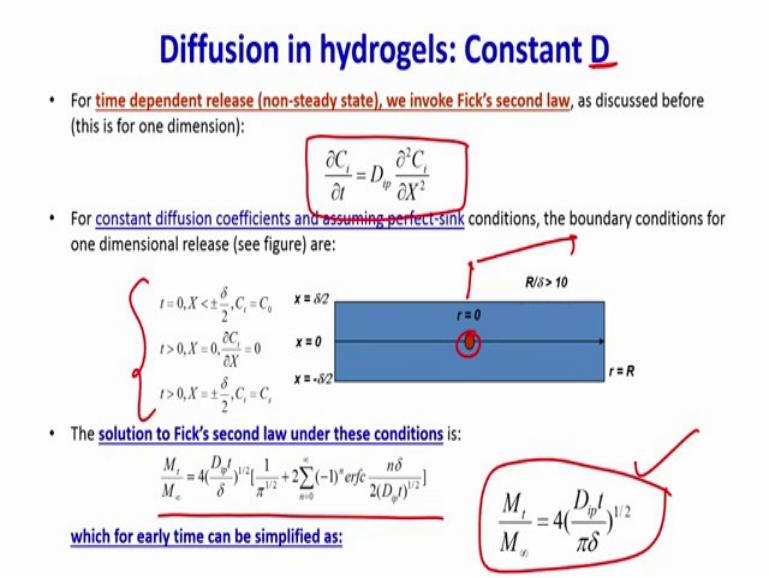
(Refer Slide Time: 18:19)



Then, the next thing comes about the diffusion the hydrogel. So, let us say the pores are big enough or the pores are not big enough; how it is does it refuse from such a system? So, release of drug and solute from the hydrogel matrices is defined by the diffusion into the polymer in that, polymer network. So, there are mass transfer limitations due to the network structure itself. So, it is necessary to understand what is the fundamental mechanism of this transport. So, it is a diffusion control release, we can use the Fick's law right; we can just write the Fick's law, where the

$$J_i = -D_{ip}\frac{dC_i}{dX}$$

(Refer Slide Time: 18:55)



So, that is to start with; so, let us say that, the diffusion in hydrogel, there is a constant D that we are going to consider. So, for time dependent release we will basically invoke the second law, so which is then defined by this in one dimension. So, if the diffusion coefficients are constant and we are assuming that, outside whatever the drug is going to come out outside is going to immediately gets sucked away, then, we can define the boundary conditions here, as is defined here

$$t = 0, X < \pm\frac{\delta}{2}, C_i = C_0$$

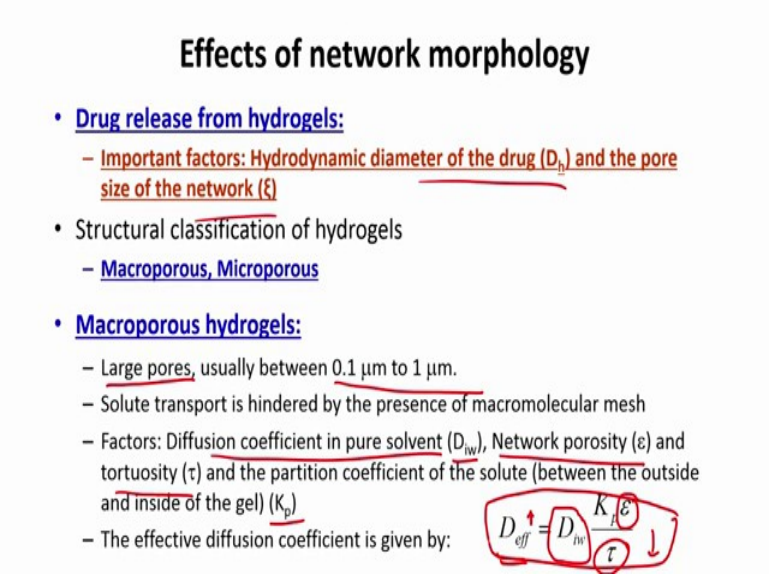
$$t > 0, X = 0, \frac{\partial C_i}{\partial X} = 0$$

$$t > 0, X = \pm\frac{\delta}{2}, C_i = C_s$$

So, we put this all, we get a Fick's law solution, which is this and if we only consider early time points, we can neglect few of the terms and then we get the release would be like this. I hope this is understood, again we do not need to go into the derivations of these differential equations, but using the Fick's law and putting in the boundary conditions, we are getting a solution which looks like this. And at early time points, we can then, simplify it using this and early time point is most important as I said the

hydrogels do not really release it drug for too long. So, we will just talk only about the early time point here.

(Refer Slide Time: 20:26)



So, now how does the network morphology affect this; I mean so again, in the previous case we had not really taken into account anything that has to do with the hydrogel. So, how does the role that, now it is in the hydrogel plays? So now, that the drug is released from the hydrogel, the drug diameter as well as the size of the network becomes important. So, we can now classify the hydrogels in different forms, it could be macro porous or micro porous. So, as the name suggests what is macroporous?

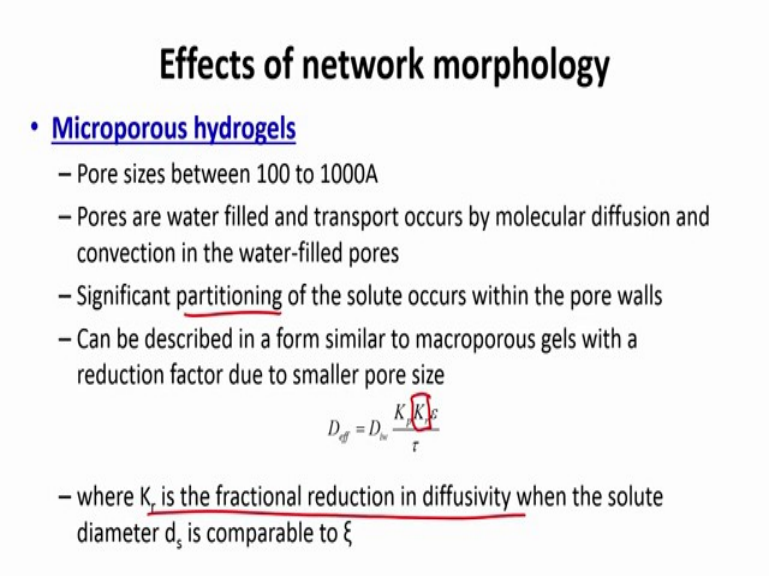
Macroporous essentially mean, it is large pores, macro pores, typically for biologically relevant things we were talking about 100 nanometer to about a micron. So, the solute transport is hindered by the presence of the molecular mesh of course, the drug is going to collide with the mesh as well and so, the different factors that, we can then introduce is one is the diffusion coefficient in the pure solvent

So, let us say, if there was no mesh; then, the diffusion coefficient would have been Diw now, the another thing we are defining is network porosity that we have already defined and tortuosity and then, now the drug may have some partition coefficient right; because, it may have a different solubility between the outside water as well as inside the gel. So, let us say that, partition coefficient is defined as Kp, then we can use these terms to modify the equation that, we just listed in the last slide and the way we will modify that

is we will say that, the Deffective is; now, we are saying that D is not constant right. So, we are saying the Deffective is then, gets multiplied by first of all the partition coefficient of D in the solvent, then what is the network porosity?

So, higher this is the higher this term is, higher the tortuosity the lower and the Deffective will be. So, this essentially, becomes a Deffective. So, that is the new Deffective and now, this Deffective is going to change locally there micro domains, but will neglect that for now.

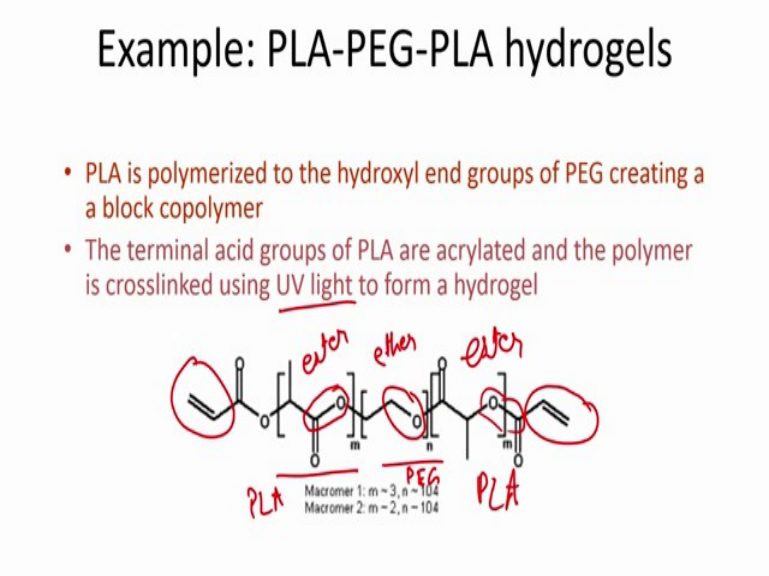
(Refer Slide Time: 22:26)



What about a micro porous hydrogel. So, as the name suggests micro pores are essentially, we are talking about smaller pores they are not as big as, what we defined earlier. So, these could be 100 Armstrong to 1000 Armstrong or even smaller. So, these pores are water filled and the transport across this is essentially by molecular diffusion and convection in the water filled pores; there is a lot of partitioning, that is going to happen on the solute within the these pore walls and this can be described in a form similar to the macroporous gels with the reduction factor.

So, now, we are saying that this essentially this partition coefficient, is going to change and there is another reduction factor Kr that, we are adding, which is a fractional reduction of the diffusivity when the solute diameter is comparable right; because, now there is a lot more collisions, that is going to happen between the chains and the drug, that is being used to deliver.

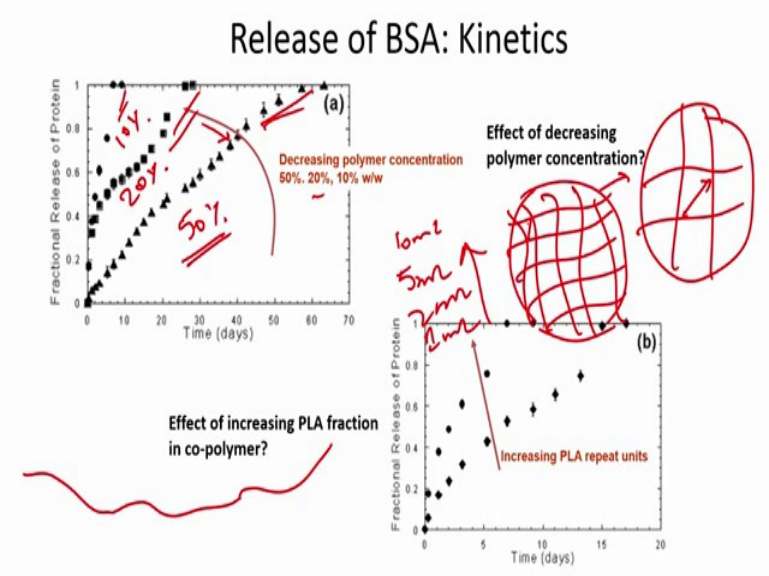
(Refer Slide Time: 23:26)



So, an example; so, here we are talking about a PLA PEG PLA hydrogel. So, as the name suggests. So, we have a PLA domain, remember PLA is lactic acid polymer. So, therefore, these ester groups; we have a PEG domain and then, we have again this ester domain with PLA; this is you can see the ether domain. So, let us see, in this example we are saying that, the terminal acid group has now been modified with acrylate group. So, what does acrylate do from our past discussions? It can get activated from free radicals in the presence of UV light.

So, when the light shines on it, what will happen, is these acrylate bonds will get radically polymerized by reacting with the other activated acrylate groups.

(Refer Slide Time: 24:36)



So, let us talk about some of the release from this is actual data from some papers. So, what they did is, you can see, they got a certain release over a certain time. So, this is the release of the protein, that was encapsulated and this is on the basis of time. So, as you are decreasing the polymer concentration from 50 percent to 20 percent to 10 percent, what you are saying is the release is increasing right. So, let us say, this is 50 percent, this is 20 percent and this is 10 percent.

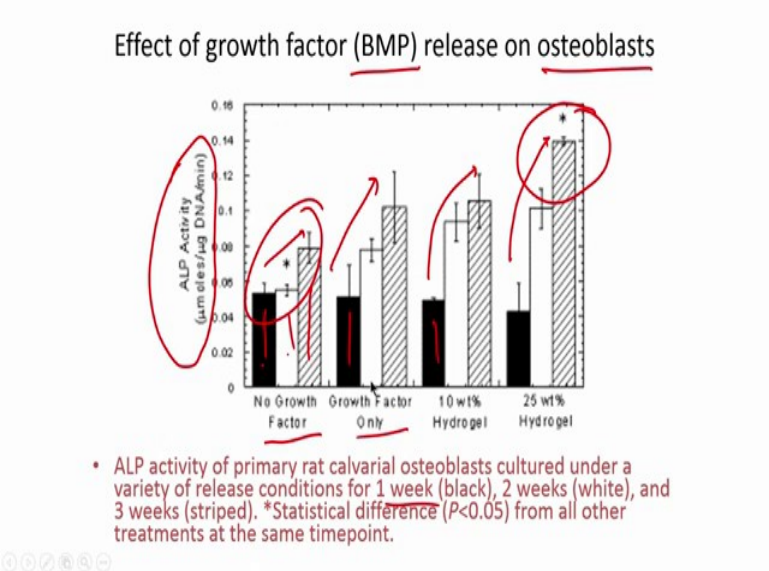
So, what does that mean; that means, when I say 50 percent; that means that, the polymer is about 50 percent in the whole volume right. So, almost let us say, if I make a 10 ml gel then, I am saying 5 ml of that is the polymer itself or 2 ml of that is a polymer for 20 percent and then, similarly, 1 ml of that is a polymer. So, what we are saying is the chains are becoming more and more dense as you are increasing the polymer concentration. So, what will happen, if there are more chains in a confined area? That will, what will happen is let us say, I have these chains and if I increase the polymer density within this area now, instead of having two chains, I will have four chains or five chains.

So, what has happened is the pore size has decreased quite a bit. So, that is has been reflected in the release rate because, now that, the pores has decreased quite a bit its causing it to in this direction its slowing down whereas, if you go in this direction, where you are decreasing the polymer concentration then, more and more BSA is coming out

very rapidly. So, as you can say for this 50 percent gel in this particular case for BSA, it took about almost 50, 60 days for all of the amount to come out whereas, as you are decreasing it, this is now changed to 20 days or 10 days for 10 percent. What is going to be the effect of increasing PLA fraction? So, what will happen now, if I increase the PLA?

So, what is PLA in this case? When I am saying the fraction I am saying that, essentially the PEG component is the same, but the PLA that is attached to it has increased. So, this is going to increase the molecular length of this. So, what will happen? As I increase the PLA units; now, I am talking about longer chains right and so, because these are longer chains what will happen is; now, the release rate is actually going to increase, as I am increasing the PLA. So, this is going to basically, cause the proteins to come out even faster. Here is another example.

(Refer Slide Time: 27:19)



So, in this case, they have used BMP, which is a Bone Morphogenic Protein, very widely used for bone regeneration applications and osteoblasts are nothing, but cells of the bones, that involved in bone formation activity. ALP is a measure of how much bone they are forming. So, it is an enzyme, that if the more bone is being formed the more enzyme will be there and so, you can see there are three cases here; so, each of these bars are; so, the black bars are one week data the white bars are 2 week data and the hash bars are essentially, striped bars are 3 weeks data.

And so, what you can see you can have a hydrogel and you just have cells in 2 D and you will have a certain amount of ALP activity another time progresses. So, limited amount here, you can add just the growth factors to them and this increases a bit of the bone formation these growth factors, which is essentially BMP here.

You can put it in a hydrogel and now, because it is in the hydrogel itself, that itself because, this is a more closer environment to what they see in 3 D the cells are itself compared to this guy, the cells are increasing the bone formation and now, if you put further the BMP in here, that is going to further increase the bone formation. Now, because the BMP slowly being released and its being used by these cells to form these bone. So, we will stop here, we will continue in the next class and I am going to talk more about hydrogels and in the next class we talked about in situ hydrogels. So, see you then.

Thank you.