Drug Delivery Principles and Engineering
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Lecture – 17
Hydrogels – III

Hello everyone, welcome to another lecture for Drug Delivery Engineering and Principles. Let us do a quick recap of what we did in the last class.

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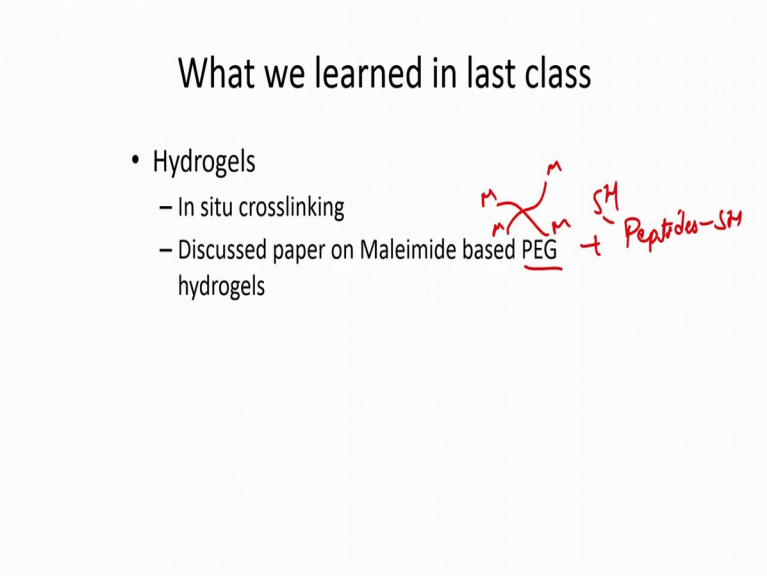

So, we are continuing our discussions on hydrogels, as we discussed, what are hydrogels? Hydrogels are these highly hydrophilic gels, that are made from hydrophilic polymers and they have the capability to absorb lots and lots of water and they can swell.

So, why they are very important is because first of all they are very similar to how the tissue normally is. So, if you look at the tissue lots of ECM components are hydrogels themselves, they are extremely hydrophilic and they are encapsulating all kinds of cells where cells then use various processes to synthesize more ECM as well as do their normal functioning.

So, within the hydrogels, we had discussed quite a lot of variations of them, we discussed physical, we had discussed the chemical and then we also discussed ionic hydrogels and then we further went ahead in the last class and we talked about in situ

crosslinking gels. And so what are these in situ crosslinking gels? It means, that they crosslink at the site and interest of the site for our application is the human body or anybody.

So, in that sense; that means, that when we inject these hydrogel precursors, which are typically in liquid formulations into the body, they will crosslink right then and there and this could be on the basis of several thing, this could be on the basis of time, this could be on the basis of temperature, so all of these are fairly feasible. And then we discussed a paper in which maleimide was used as one of the crosslinking method for making hydrogel.

So, these are PEG based hydrogels that we talked about and maleimide was one of the chemical group that was reacting with thiols. So, this was PEG which is reacting with peptides, that had thiols on both ends and that and this PEG was of course, the four arm PEG with maleimide at the four ends.

And that essentially led to crosslinking and what we found was basically there were several chemistries that can lead to the production of the hydrogels, but among the four five moieties that this group had compared, they found that maleimide was by far the most efficient as well as well suited for any in situ applications as well because the gel was then able to cross link and then adhere to the tissue as well.

So, now that we have described all this we are going to discuss some of the maths today as to how we can compute what is the pore size, what is the different formulations that leads to different pore sizes. So, how do we go about doing that?

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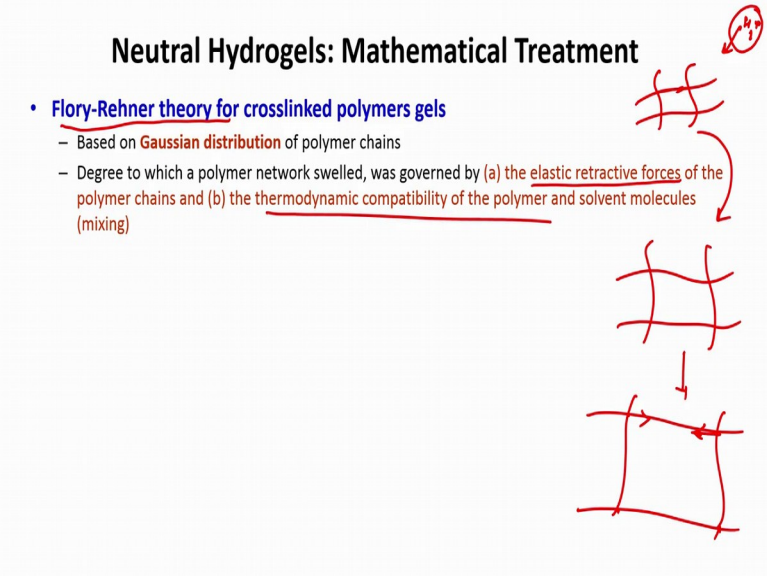

So, for the purpose of this class we are only going to talk about neutral hydrogels and we are going to define three of the terms and give the equations as we go along in today. So, the first thing is the Flory Rehner theory and what it is? It is basically a theory that defines how the crosslinking of the polymers gel happens. So, what they are proposing is there is a Gaussian distribution the polymer chains that is found in nature and that is a good assumption to make given what we see in the literature. And the degree to which a polymer network will swell is going to be governed by the elastic retractive forces of the polymer chains as well the thermodynamic compatibility of the polymer.

And, so what essentially this means is let us say I have a polymer that is crosslinked. So, now, as I said these are hydrogels and they tend to absorb water, but there is some limitations to it, of course, thermodynamically its favourable for the water to go in and interact with these polymeric chains. So, that is where the thermodynamic compatibility of the polymer comes from, whereas, as it continues to observe water, these chains here will get stretched.

So, eventually this is going to get to a formation like this and let us say if they continue to stretch they going to get to formation like this, but eventually these chains themselves will start to have tensions because; obviously, they are sort of crosslinked at these sites and there is a limitation to the amount that these can be stretched. So, that is where the elastic retractive forces come in.

So, now these chains are going to try to bring this polymer gel back to its original state and so its the force balance between these two forces the affinity for the water to get absorbed into the system, as well as the elastic retracive forces of these chains to sort of resist that and go back to their origin state. So, essentially that is what will define is at what stage at equilibrium the hydrogen will stop right. So, now, that we have that concept clear.

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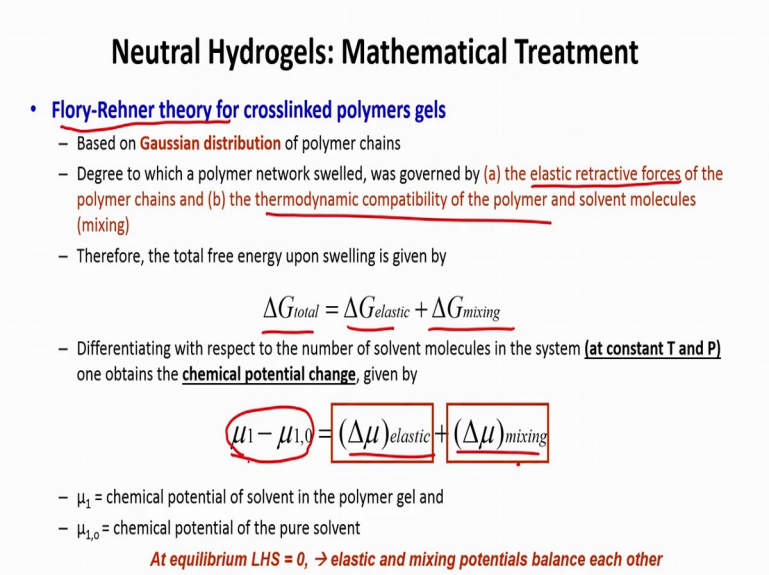

So, therefore, the total free energy upon swelling will be given by what? Will essentially be the total free energy will be equal to the free energy because of the elastic forces as well as the free energy because of the mixing. Now, with respect to the number of solvent molecules in the system, we are saying at a constant temperature and pressure of course, we change this, the final state of the hydrogen will change, if you increase the temperature maybe it will swell more, if you change the pressure maybe it will swell more or less depending on what you are doing with the pressure.

So, we can then essentially convert this deltaG to delta μ which is the chemical potential change and we can basically say that whatever change we have seen in the chemical potential will be equal to the change in potential due to elastic as well as the change in potential due to mixing and the mixing is of course, the thermodynamic mixing of the water with the polymer chains. So, again as I said the μ1 is a chemical potential of the solvent in the polymer gel as well as μ1,0 is chemical potential in the pure solvents.

So, we are assuming that it was formed in the pure solvent and then it is mixed into this new solvent now, within the polymer gel now. So, but we know at equilibrium, it would not really change its state. So, basically it would have attained already this balance between these two forces. So, we know that at equilibrium, the left hand term which is the change in the potential will become zero. So, that means, then the elastic and the mixing chemical potential change will have to be equal to, so that they balance each other out.

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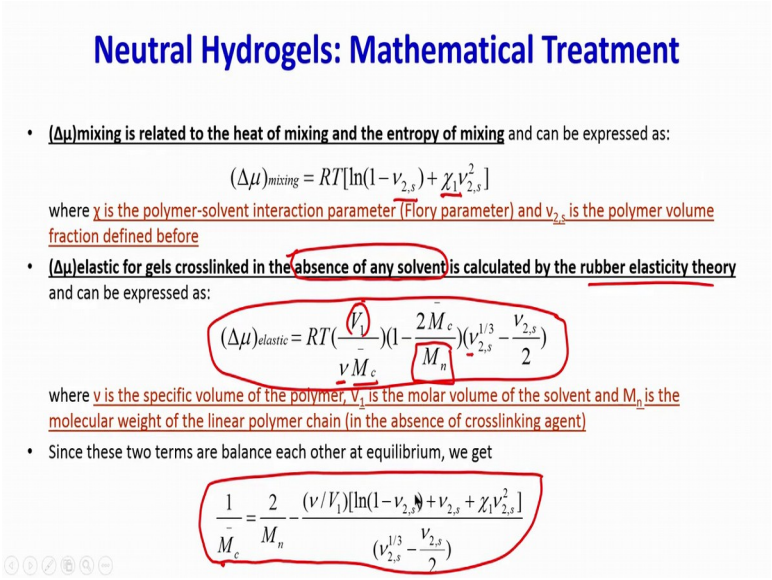

So, now that we have established that, let us see how we can define the delta μ for mixing. So, this is of course, related to the heat of mixing and entropy of mixing. So, this can be defined directly as delta μ mixing is equal to the RT with this expression. I am not going to go into the derivation of all of these equations. So, where we know that the chi is the polymer solvent interaction so, how the polymer and solvent are interacting.

So, this is going to change if you change the polymer, this is going to change if you change the solvent. And then V2s we have already defined before is nothing, but the polymer volume fraction of the gel. What about the elastic chemical potential change? So for crosslinked gel in absence of any solvent is calculated by that rubber elasticity theory.

So, of course, this case with we saying in the absence of any solvent is sort of nonexistent because the hydrogel will only form when there is some sort of solvent you

cannot expect just the polymer chains to just mix because there will be no diffusion, no sort of interactions happening. So, this is just an hypothetical case for now, but the delta μ elastic for these gels will essentially be calculated by the rubber elasticity theory and this can be expressed as delta μ elastic is then expressed as this term where again now we have defined couple of terms. So, this is the specific volume of the polymer.

So, what is the specific volume of the polymer itself V1 is the molar volume of the solvent, so it then define this how much of the solvent is there. Mn is the molecular weight of the linear polymer chain, so this is essentially how big your chain is of course, that is going to help with that and what is Mc? Mc we had defined before is that distance between the crosslink.

So, essentially as we discussed in the last slide, they have to balance out each other since these two terms should balance at equilibrium. We can then equate and sort of solve for what is the Mc with other terms and again Mc was the length between the cross links, the average length between the cross links.

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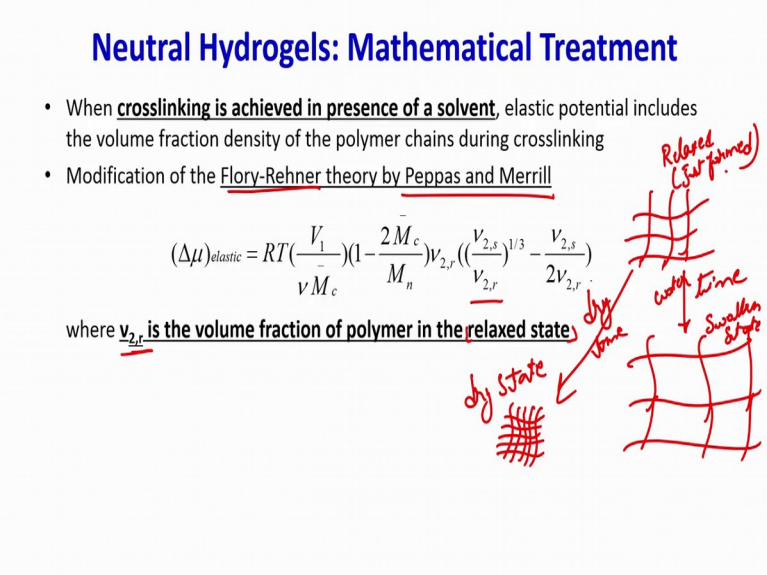

So, now that we have this mathematical term; as we already said in the previous slide that this is in the absence of any solvent and this is not really any physiologically relevant, this all the crosslinking in the hydrogel you will see is going to be in presence of some solvent.

So, now if I add the solvent and try to correct this equation to reflect that, what I will do is, this was done by modification to the Flory Rehner theory by Peppas and Merrill and what is done is we have to include the volume fraction density of the polymer chains during crosslinking. So, we have defined a new term called v2r which is essentially the volume fraction of the polymer in that relaxed state and when I say relaxed state, what is the relaxed state? So, let us say if I am doing the synthesis of the hydrogel in let us say 100 micro liter of a solution and the hydrogel is formed. Then as when it is immediately formed what is the sort of the volume polymer fraction at that state.

So, this is a relaxed state, which essentially is just formed. Obviously, as more and more time is given this, because it wants to interact more with the water, will essentially starts to swell and at some equilibrium it will stop. So, we can call this one as a swollen state. Or alternately what we can do is we can let it dry off, we can use some high vacuum or we can just dry it in the air and so this is dry over time, this was time in water. So, if I let it dry off these polymer chains will further collapse and this is actually nothing, but dry state.

So, we have just defined relaxed state, swollen state and dry state; obviously, in dry state if we are saying that we completely dry it off, that there is no water present what will that give you that will essentially give you what amount of weight did you actually started with. So, so these are the couple of terms, but basically that previous equation for μ elastic then gets corrected by this term of v2r, so which is then reflected here.

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Neutral Hydrogels: Mathematical Treatment

- When **crosslinking is achieved in presence of a solvent**, elastic potential includes the volume fraction density of the polymer chains during crosslinking
- Modification of the Flory-Rehner theory by Peppas and Merrill

$$(\Delta\mu)_{elastic} = RT\left(\frac{V_1}{\nu \bar{M}_c}\right)\left(1-\frac{2\bar{M}_c}{M_n}\right)\nu_{2,r}\left(\left(\frac{\nu_{2,s}}{\nu_{2,r}}\right)^{1/3}-\frac{\nu_{2,s}}{2\nu_{2,r}}\right)$$

where $\nu_{2,r}$ **is the volume fraction of polymer in the relaxed state**

- Relaxed state → immediately after crosslinking but before swelling
- Equating the (Δμ)mixing with this new (Δμ)elastic one gets

$$\frac{1}{\bar{M}_c} = \frac{2}{M_n} - \frac{(\nu/V_1)[\ln(1-\nu_{2,s})+\nu_{2,s}+\chi_1\nu_{2,s}^2]}{\nu_{2,r}\left[\left(\nu_{2,s}/\nu_{2,r}\right)^{1/3}-\frac{\nu_{2,s}}{2\nu_{2,r}}\right]}$$

So, again relax state is basically immediately after crosslinking, but before swelling. So, then we can now equate the delta μ mixing with the delta μ elastic like we did in the last slide just because it has to be balancing each other out at equilibrium state and then what we get is essentially, a modified equation which then defines Mc as a function of several other parameters that we can compute or determine using various techniques.

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Rubber Elasticity Theory

- Hydrogels: **Similar to natural rubbers** → responds to applied stresses instantaneously.
- **Ability to deform readily under low stresses and for** < 20% deformations can fully recover rapidly → **ELASTIC**
- Originally developed by Treolar and Flory for vulcanized rubber and later modified by Flory. → does not apply to hydrogels prepared in presence of solvents
- Modified by **Peppas and Merrill**:

$$\tau = \frac{\rho RT}{\bar{M}_c}\left(1-\frac{2\bar{M}_c}{M_n}\right)\left(\alpha-\frac{1}{\alpha^2}\right)\left(\frac{\nu_{2,s}}{\nu_{2,r}}\right)^{1/3}$$

where τ is the stress applied to the polymer sample, ρ is the density of the polymer and R, T and Mc have their usual meanings.

- The term α **represents the "elongation factor" due to the applied stress.**
- A tensile testing apparatus is used to measure rubber elasticity for hydrogel samples

So, continuing further with the rubber elasticity theory, so hydrogels, these are again similar to natural rubbers. So, the ability to deform is high under low stresses and can be changed, so they can be considered to be elastic essentially. So, right now we are talking about how this rubber elasticity came up. So, we are saying that for deformations which

are less than 20 percent, we can say that these are elastic deformations and this was originally developed by Treolar and Flory for rubber and then was later modified by the Flory to reflect it for hydrogels.

And again as I said that, that theory was developed initially to reflect the change in absence of solvents and then it was further modified by Peppas and Merrill and with the rubber elasticity theory, they are saying that if tau is the stress applied to the polymer sample and rho is the density of the polymer itself, then you can sort of equate them on the basis of this equation.

So, now we have another equation, so tau is something that we are applying the stress for, so we can use some instruments like rheometer and all to know what is the tau and that will give us another equation along with the last equation to be able to get some idea as to what are the different Mc and v2s and v2r. And then again alpha here represents the elongation term, so this is basically the elongation due to the applied stress and as I said the tensile testing apparatus can be used to measure these rubber elasticity for hydrogel samples.

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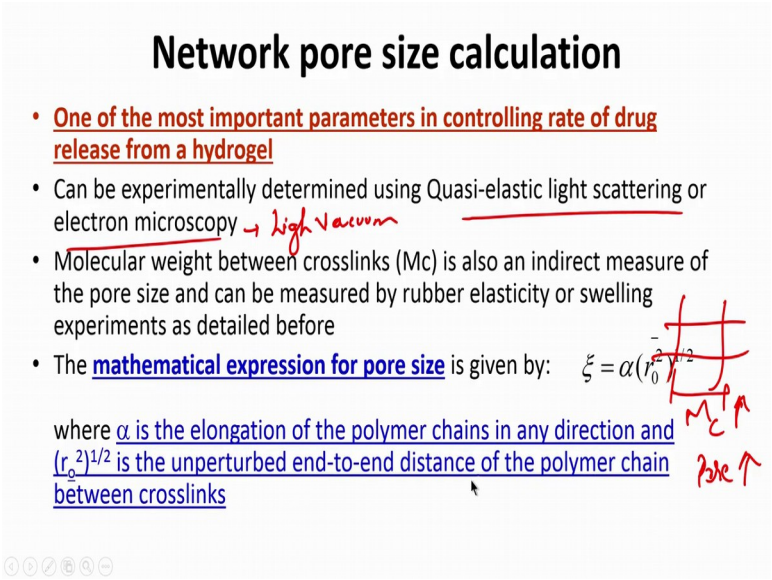

So, now to do what is the pore size calculation which is what eventually we want to get at. So, again this is the one of the most important parameters in controlling the rate of drug release from hydrogel right because if I have for the same drug and for the same concentration if I change the pore size from let us say 10 nanometer to 15 nanometer,

now it will be much easier for drug to diffuse out from the hydrogel network, then it will be when the pore size is low. And so that is one of the most important parameter that we have to define. I cannot really try to deliver let us say a drug which is 15 nanometers in diameter through a hydrogel that only has pores of 10 nanometer because those drug molecules will not be able to even physically come out from the hydrogel.

So, this is something that we definitely need to define and then we can directly measure that using some techniques like electron microscopy or light scattering, the problem with the electron microscopy is this is typically done in high vacuum. So, even though you will get some idea as to what is the pore size, but then since this is done in high vacuum, this is essentially giving your pore size in dry state. However, when we put this hydrogel in the body or use it at for any biological applications, its always going to be in aqueous media.

And now since it is in aqueous media this pore size will change because it has much more water around it there is going to be swelling and all that and so the value you will get is not going to be accurate, so you cannot really trust this high vacuum data for the pore size. Even though you can then use this to compare between different hydrogels, but that comparison will also have some caveats to it.

So, as we said the molecular weight between crosslinks is an indirect measure to the pore size right I mean if I am saying that, if this length is Mc as this length increases the pore size will also increase. So, it is some measure for that, so the mathematical expression of the pore size is then given by

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

So, basically the root mean square of that which is the unperturbed end to end distance between the polymer chains. So, essentially this is Mc itself, but define in some other way, so that its always positive.

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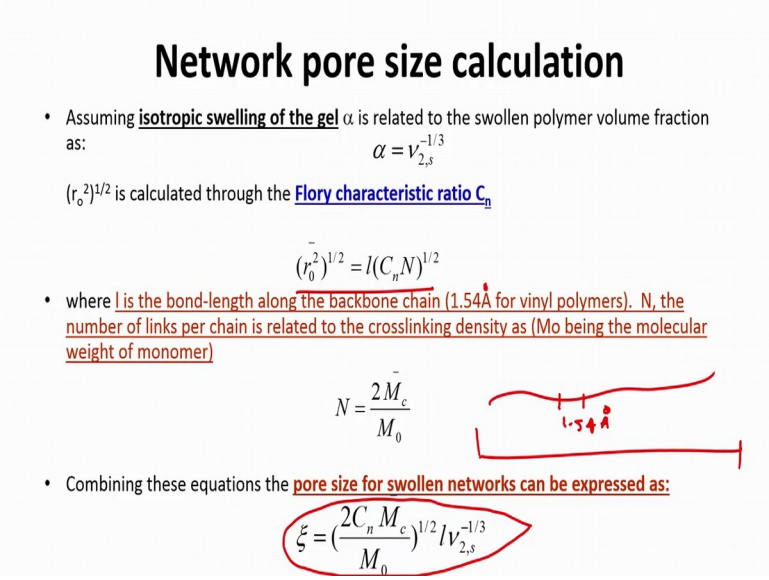

So, now assuming that and assuming that there is isotropic swelling of the gel, so; that means, that let us say if this is the swelling, then its happening isotropically, which means that all these lengths will increase rather than just having an increase like this, I am saying that this is wrong, but this is correct, this is isotropic swelling and that is a good assumption to make unless there is some inhomogeneity in the gel.

So, if I assume that then what we can say is that the alpha which is the elongation is nothing, but it is going to be proportional to the cube root, the negative cube root of the v2s which is the volume fraction in the solvent. And then the r naught is calculate through the flory characteristic ratio N which is then defined empirically like this where l is the bond length along the backbone.

So, typically 1.5 to 1.7 angstrom for different polymers, here is an example of 1.4 angstrom for vinyl polymers and N is the number of links per chain. So, if I know what is the bond length I am saying there are N number of links per chain which is related to the crosslinking density as well. So, M0 being the molecular weight of the monomer, will come this will turn into

$$N = \frac{2\bar{M}_c}{M_0}$$

So, essentially we are saying if this is the chain and between the backbone, each bond is let us say 1.54 angstrom this for the vinyl polymers and is the number of links per chain. So, how many links of such are there, then we can sort of define N as the 2M c by M 0, where M0 is basically the total molecular weight of the chain.

So, if I combine these two equations the pore size of the swollen networks and then we expressed as, so, all I am doing is recombining the previous equations with these equations and what I will get is a value for the pore size defined with some other terms and that is how I can then find what is the pore size of my hydrogels.

So, quite a complex calculation up to here, but then I will give you an example now of what it is typically done in the field if you are making a hydrogel, which will make it simpler.

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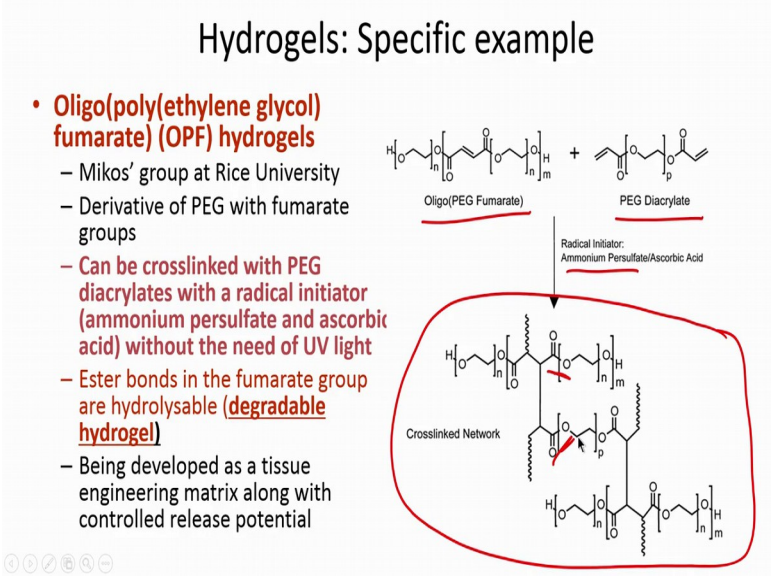

So, here is a specific example. So this is specific example is looking at polymerization of two different types of PEG. So, you have an oligo PEG fumarate and a PEG diacrylate, it is again a radical reaction you use some initiator, so in this case ammonium persulfate. And what will happen is these radical bonds will start to react with the PEG fumarate essentially leading to a crosslinked network which is defined here.

So this is of course, example from Miko's group at Rice University in US and what they have done is they form hydrogels which they have called OPF hydrogels. And the PEG

diacrylates can be used by a radical initiator like ammonium persulfate ithout the need of UV light and then the ester bonds ester bonds at a form which are again hydrolyzable. So, all of these ester bonds, these can be degraded by water and the original purpose of this hydrogel is to kind of use it as a tissue mimic sort of use as controlled release potential as engineering matrixes at all.

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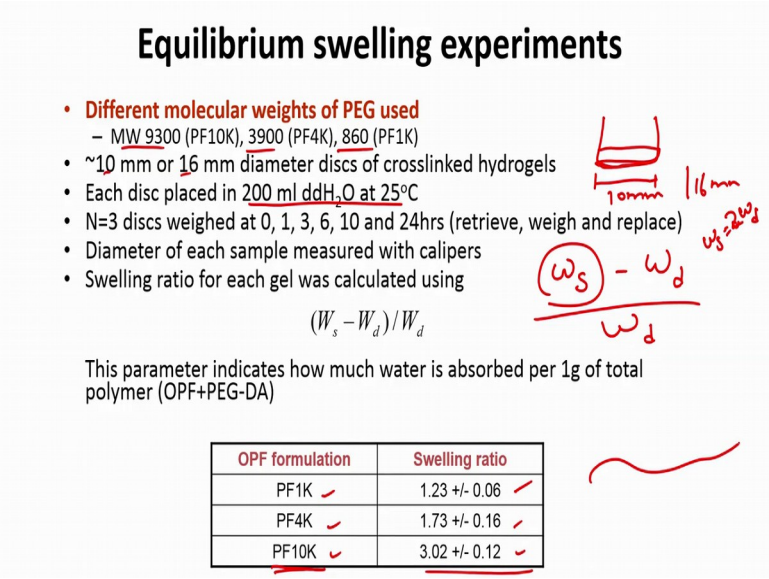

So, let us see what they have done in terms of characterizing, what is the pore size of this particular hydrogel that they have formed. So, what they did is for the PEG they have different molecular weights PEG that they have use. So, they form three different types of gels defined as PF10K, PF4K, PF1K and that is essentially telling you what is the length of the PEG that they used.

And then what they did is just to form the gel they use these cell culture plates which typically have wells and depending on how big that cell culture plate is, these wells can be 10 millimeter, 16 millimeter or something else, in this case they have used 10 and 16 millimeter discs. And then once they have formed it, so that is the relaxed state and then what they have done is then taken these discs because now the hydrogel acquires whatever shape was there and this is a disc shape. So, they are now taken these discs and placed it into a very large volume relatively compared to the gel size of water at 25 degree Celsius.

And then what they did is over time they have done experiments. So at the time the disc were formed at time 0, they have weighed that and then they have continued to weigh it at different times right and then they have also measured the diameter which is basically using calipers already defined here is 10 millimeter or 16 millimeter.

So, now how do you calculate the swelling ratio, so you are saying that if it is swelled it is because lots and lots of water had went in. So, we are saying that because the water went in, after swelling there is a certain weight Ws and before swelling there is a certain weight Wd and then the ratio is basically how much it has swelled. If it swelled twice, then what has happened is now we have a swelling ratio of one, so it has become double the size.

And so now they have determined and what they found is if they are using a 1K, 4K or 10K they find that the swelling ratio is different and notice how as you are increasing the molecular weight of the chain, this swelling ratio is dramatically increasing, right, it is it is become all the way up to 3 as you have increased the molecular weight of the chain that you are using.

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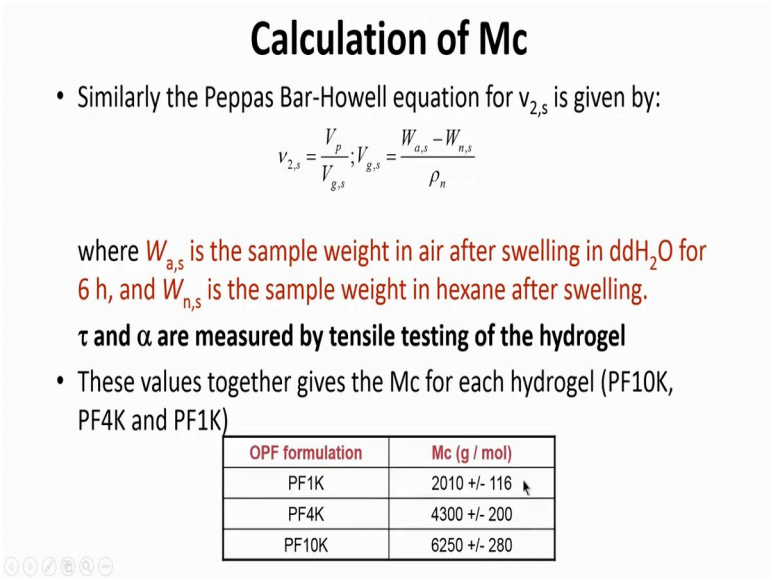

So, now they can apply the Peppas Merrill equation for Mc and again just reiterating it here; here is the tau right. So, now, if they want to apply that there are several parameters that they do not know, what is v2s, what is v2r, so these are easy to find out. So, what they can do is, they can use the hanging pan and measure this, so v2r is nothing, but

weight of the polymer divided by the weight of this term and then similarly Vp which is the one of the polymer is nothing, but how much you have added the water divided by the density. So, once you apply all these equations and get some of the values from different parameters reported in the literature, you can do this in different solvents as well, you can do this in hexane.

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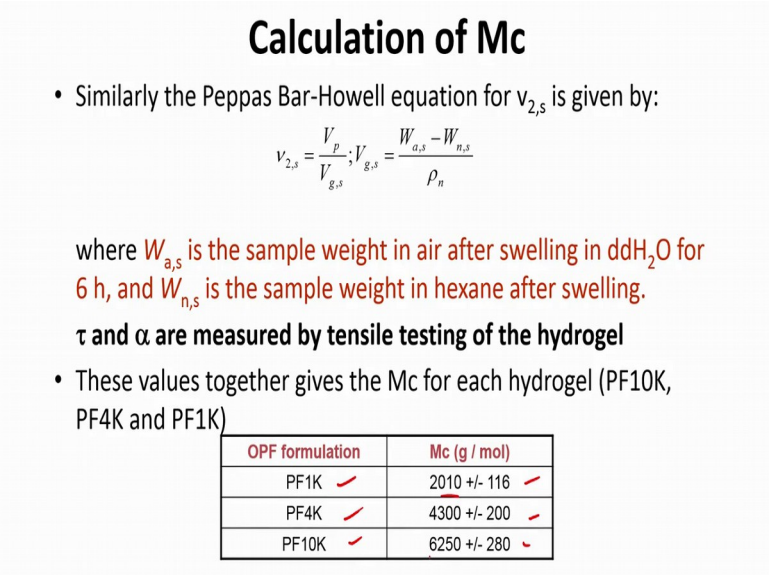

And so what you end up with is essentially applying and fitting all these value you get an Mc for different gels. So, you have PF1K, PF4K, PF10K and notice how the molecular weight between crosslink has also increased. So, it does went all the way from 2000 grams per mole to 6250 grams per mole.

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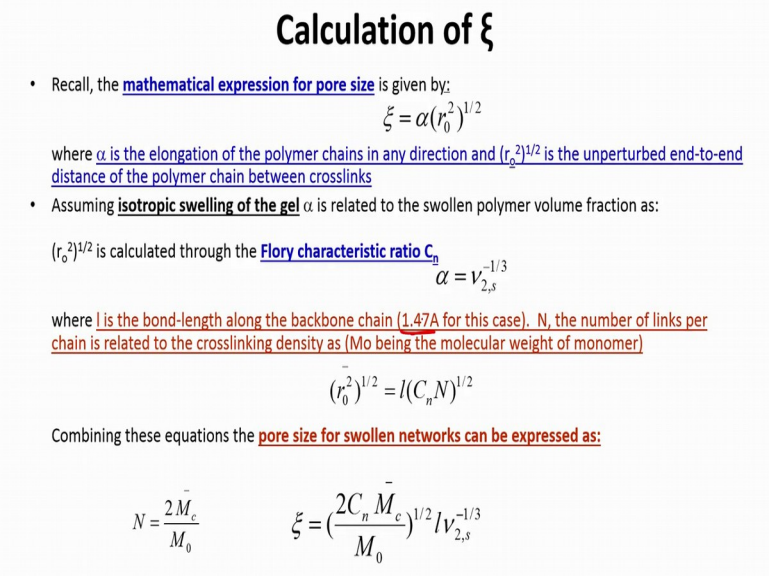

And then once you have that you can just directly put this into the pore size calculation and essentially just apply this throughout, where we have 1.47 is the angstrom length between these polymer bonds in the backbone.

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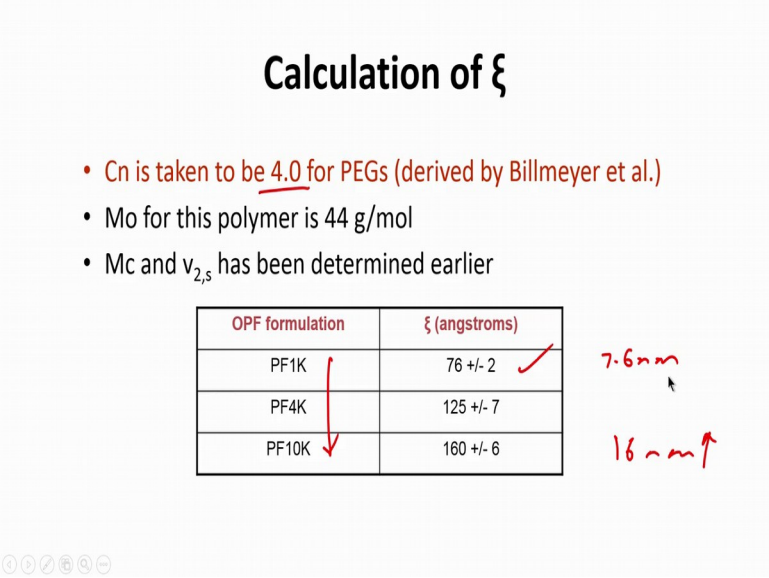

So, if you apply that what you will find and Cn is basically taken from the literature and what you will find is the pore sizes increases from 76 angstrom which is essentially 7.6 nanometer to 16 nanometer. So, this sort of reiterates if that if you increase the molecular weight of the polymer itself you will get a higher pore size.

So, we will stop here, these are some of the terms that we have used to define what is the pore size, what is the molecular weight between crosslink. Lots of complex equations here we have assumed some of the things here as well as we have taken this equation literature and not went into the derivation. So, this is just some of the ways that you can determine what is the pore size of a hydrogel that you are making or using. We will continue in the next class.