Drug Delivery Principles and Engineering
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Lecture – 21
Nano and Micro Particles – IV

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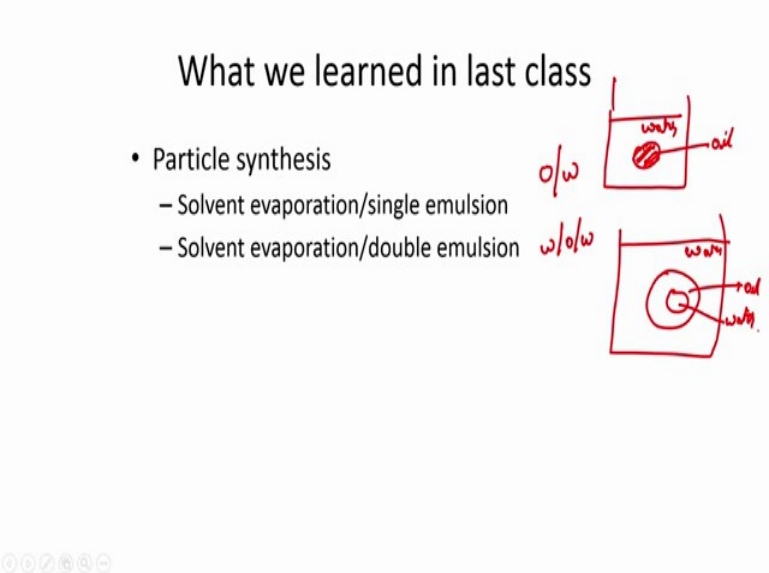

Hello everyone welcome to another lecture for Drug Delivery Engineering and Principles. So, just a quick recap of what we learned in the last class we are currently talking about particle- micro- and nanoparticles and going over some of the synthesis methods for these particles. So, we talked about particle synthesis - in that we basically covered two things one is solvent evaporation by a single emulsion method, so that is oil in water and then the other thing we talked about was a double emulsion method. So, which is nothing, but water in oil is water.

So, if I draw this schematic you will have water on the outside and oil on the inside whereas, in the water in oil in water it is a double emulsion process in which again you will have water outside and then you will have oil phase which is then encapsulating water.

So, those are the few things we talked about - we talked about some of the various parameters that are involved in making these particles, what will affect the size, what will affect their porosity and things like that and so we will continue that discussion on

particles in this class. So, one thing that I skip in the last class was the shortcomings of these methods.

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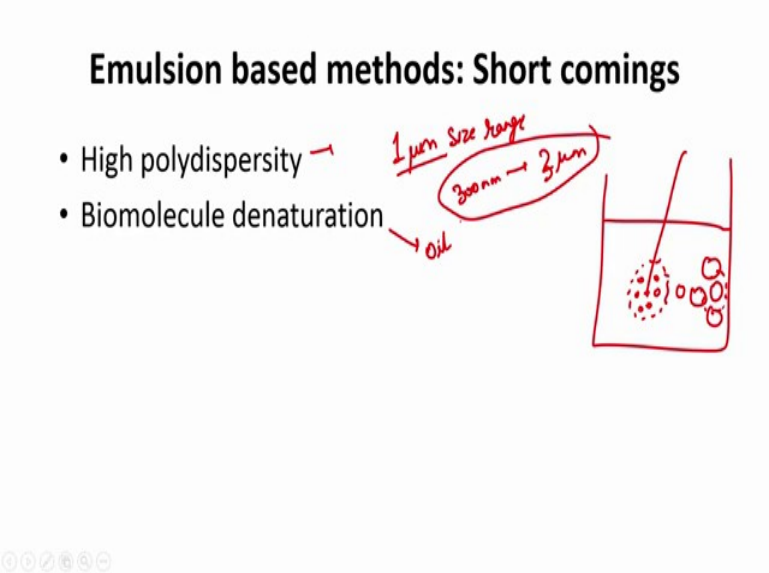

So, just very briefly first of all it results in very high polydispersity, as you saw from those images ,let us say, if you are targeting 1 micron size range you will get particles all the way from let us say 300 nanometer to all the way up to 2 or 3 microns and so it is extremely polydisperse.

So, even though your average might still be 1 micron, but you will get fairly high polydispersity in these methods and then the whole reason is because you have these emulsion based method, you can have some sort of a sonicating probe that is giving energy. So, what will happen? The particles that are in the vicinity of this probe, they will get a lot more energy than the particles which are away from this probe.

So, in these regions you will have bigger particles because they will tend to coagulate whereas, in these regions you will have smaller particles and then there will be sort of gradient through this process and that is why you will end up being highly polydisperse population.

Then the problem is you are now using oil and then oil is a completely different medium, then to what some of these biomolecules like proteins have ever seen and so these things can actually denature your whole protein structure. So, if the proteins comes in contact

with oil or other biomolecules these things are really change the structure and they may lose their activity which is again goes back to what we really wanted.

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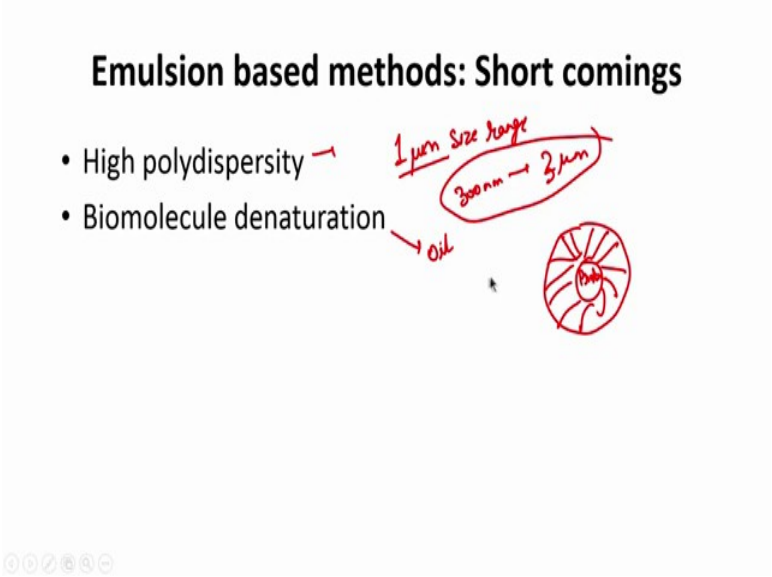

And then of course, even if it does not come in contact with oil and you have this PLGA surrounding your your proteins which are encapsulated, even now these proteins are in contact with these polymer which are again not very hydrophilic. So, the protein structure which is optimized to be what it is in the water phase may not really work very well in there and may change.

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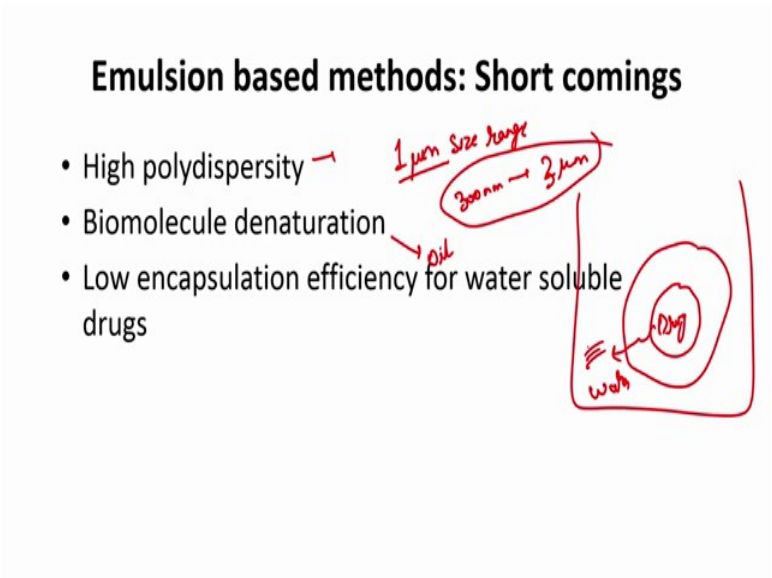

And then you typically get very low encapsulation efficiencies for the water soluble drugs. So, it is not a problem with the hydrophobic drug- the hydrophobic drugs typically get very high efficiency and in excess of 80 percent 90 percent, but when you have a water soluble drug, they have very low efficiency and the reason for that is what, the reason is of course, that once you have these particles and here's a drug and your outer phase is also water this drug can actually diffuse out into the water phase and whatever the drug that comes out is lost because ultimately you are going to pellet this particle and whatever is in this region is just lost.

So, you lose a lot of drug at the time of encapsulations and typically depends on the process and the actual parameters and the drug itself, but typically you only get about 10 to 50 percent encapsulation of water soluble drugs in a double emulsion process.

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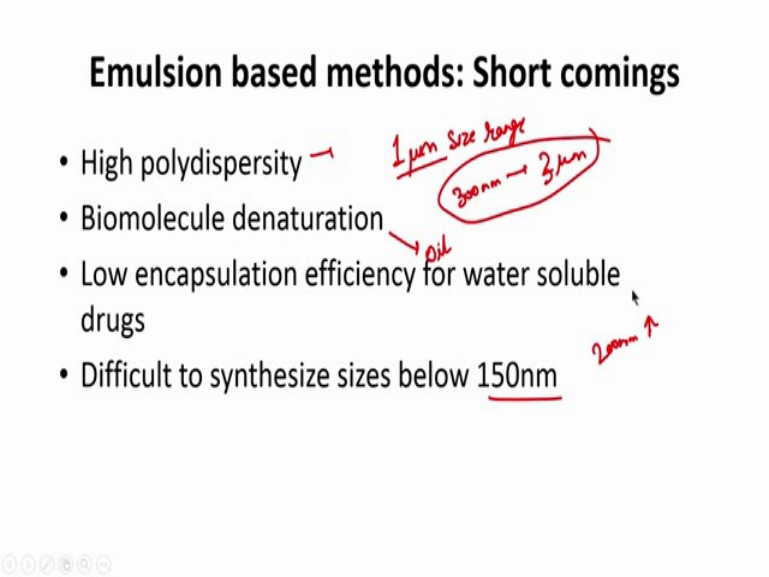

And then finally, no matter how much energy you give it becomes very difficult for you to go down below 150 nanometer. So, this works very well for anything from 200 nanometer and above, but let us say if I want particles which are much much smaller than that let us say that I want something around 50 nanometer 100 nanometer. Then these emulsion based process do not work because there is sort of limit to how much you can break down the droplet based on these energies at least with that current instruments.

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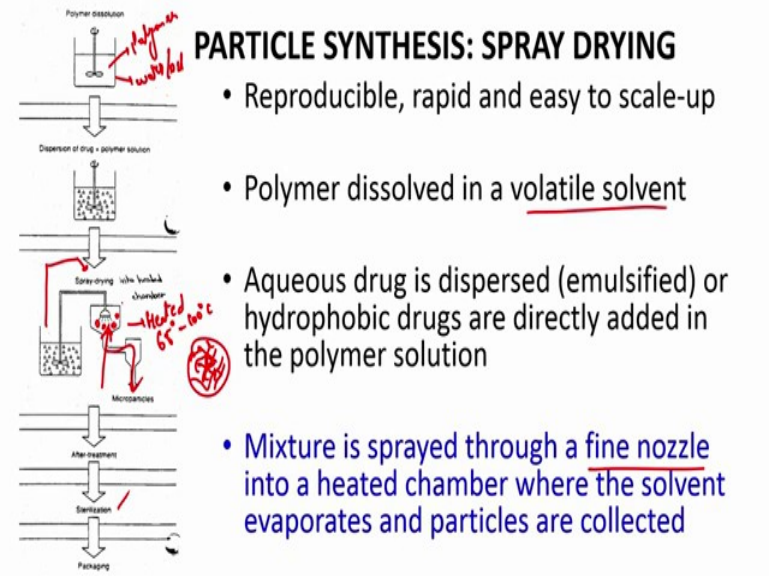

So, let us talk about some of the other methods that are being used in the field another one is called spray drying and spray drying is again very widely used method. So, what it is essentially you have your polymer that is dissolved in some phase. So, this contains polymer and then you have a then you can disperse your drug with this polymer solution. So, in this case it is in here, so this the solution can itself be either water or this can be oil it just depends on what the polymer and the drug is and where the solubilities are.

And then what you do is you mix them, so that the drug is well mixed you then spray it into a heated chamber. So, this is heated this could be heated to let us say 65 degree Celsius to 100 degree Celsius and what is going to happen is as you are heating this typically there is a this blower which is sort of blowing up heated gas and as these droplets which are being sprayed into this chamber come in contact with this heated air the solvent evaporates it could be water or it could be oil.

And the same process happens is whatever polymer chains were there in these droplets will then condense to form a particle encapsulating the drug in this case these triangles that are being shown and eventually then you can collect your particles from the outlet chamber. So, after that you can do whatever treatment you want to do, you know sterilize it, you can package it and then use it for various applications.

So, some of the advantages here are this is fairly reproducible, rapid and easy to scale up. So, since it is a continuous process you can continue to spray things in the chamber and

continue to blow air the heated air through it and you will have a continuous process and usually the scale up for the continuous process is always preferable and higher then let us say a batch process.

As I said the polymer is typically dissolved in a volatile solvent and then the drug that you are trying to encapsulate is then dispersed and emulsified, it could be a hydrophobic drug or it could be hydrophilic drug which can then which is directly solubilized in those oil based solvents. And then the mixture is then sprayed through a fine nozzle into the heated chamber where the solvent evaporates and the particles are collected.

So, of course, if I want to make smaller particles I would need to ensure that this fine nozzle is actually very fine. So, essentially the size of these droplets that are being formed in this chamber will be directly proportional to the size of the particles that we will get.

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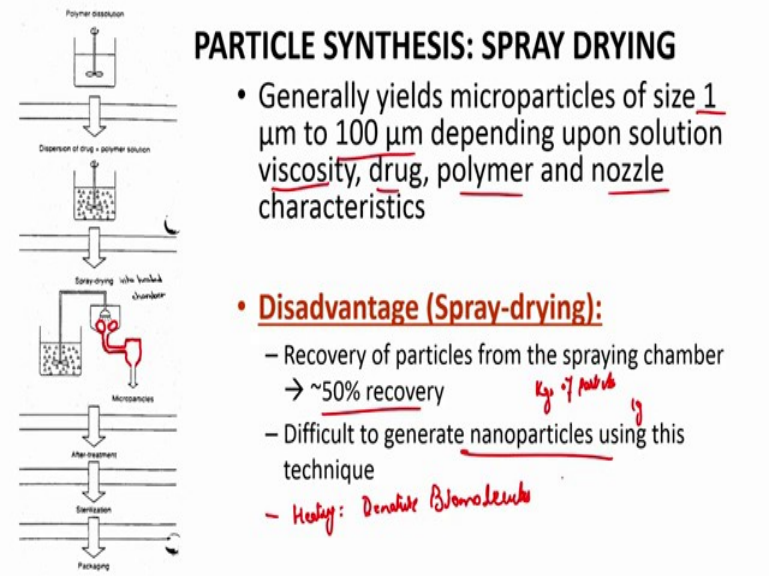

So, this generally yields particles in the size range of 1 micron to 100 micron and then it depends on several things what is the viscosity of your solvent, what is the drug in the polymer you are using and again what is the nozzle diameter. So, all of these will it ultimately determine what is the size of the droplets that are being formed and that is going to be again ,as I said, directly proportional to the amount of polymer they represent in the particle and the size.

Some of the disadvantages are the recovery of the particles from the spraying chamber can be fairly low. So, I mean now we are talking about all the surface on which the particles can stick and because of that, if you want to do a small scale synthesis you will essentially end up losing most of your particles. So, this only works at an industrial scale although there are smaller models now coming out for the lab scale even then this quite a bit of loss if you are looking for a small process small amount of particles that you want.

So, 50 percent recoveries again just sort of a random term, but it if you are making kilograms of particles, then this is much much higher, but if you are only going to make let us say 1 gram or less then you may lose quite a bit of it. And then because of the nozzle diameters and all these properties is it is actually very hard to get nano particles using this technique. So, most of the time you will end up getting only micro particles as I said between 1 to 100 micron in that size range.

So, these are some very disadvantage. Again another disadvantage that are not written is because the heating is involved. So, that can denature some of the proteins and other biomolecules. So, that is another limitation of this.

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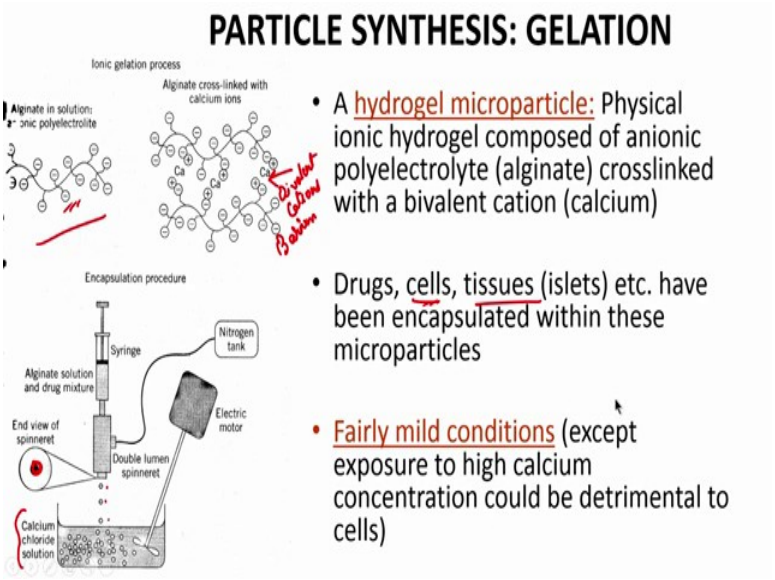

So, another method we are going to talk about is gelation. So, this is again very similar to what we talked about in hydrogels as to an ionically cross link gel, but in this case what you have is you are going to make them in a particle forms and so these are hydrogel

types of particles. So, you can have alginate which is let us say negatively charged and you can add some calcium to it which is a divalent cation.

So, you can add something else as well. These don't have to be calcium you can add magnesium, you can add some other metals which are divalent, barium is another one very widely used. And, so in this case what you have is you have a syringe containing your alginate solution and then you dispense it very controllably, very similar volumes into a solution of calcium chloride and also with some stirring to make sure that these are not coalescing. And what will happen is depending on the size of this nozzle that you have been using and the pressure conditions that are there you will get a certain size of these droplets and you can vary that with these and these parameters.

And that will essentially result in a gelation to happen anionic cross linking these polymer chains using calcium or the divalent cations. So, these are again as I said these are hydrogel micro particles because these are fairly hydrophilic polymers that are being used. Again this is widely used especially for using cells and tissues; tissues like islets small tissues that you want to encapsulate into these micro particles there will be several reasons why you may want to do that - you may want to protect them from immune system wherever you are injecting we can talk in quite a little detail about all of this as we go along in this course, but there could be a various applications for this very widely used for live cells since a very gentle process and you get a very high cell viability after the process not a whole lot of cells dye.

You cannot really use emulsion process because the moment the cells are going to come in contact with oil they are going to die. And say they are fairly mild conditions the only thing they are really putting them through is a high calcium concentration exposure sometimes could be detrimental to certain type of cells, but most of the times this is not an issue and so that is why very widely used for cells and tissue encapsulation.

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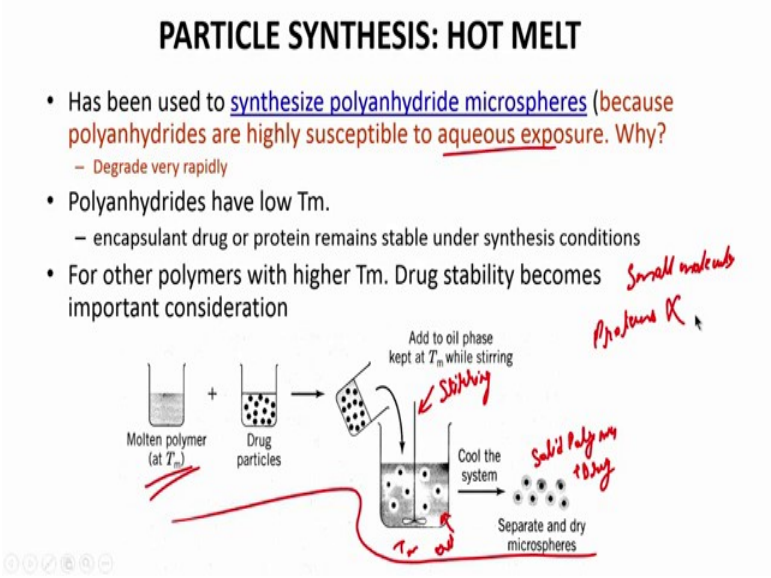

Another one that we are going to talk about is hot melt process and as the figure suggests, so you have a molten polymer at its transition temperature. So, there is no solvent involved here right now, you take your drug particles you mix them with that into an oil phase which is then stirred and kept at Tm. So, what will happen is you have these polymer which are molten containing these drug molecules and then when you cool the system down whatever the size of the particles that were present due to this stirring that will cool down and essentially result in a solid polymer with drug.

So, in this one you want to use an oil which is not really interacting with your drug itself. So, that the drug is not outside that most of the drug is going to be solubilized into the polymer directly and then you can use some centrifugation to separate this out.

So, this has been used very widely with polyanhydride microspheres and why polyanhydride is if you remember a polymer classes we had talked about how polyanhydride is very susceptible to degradation by water. So, if you expose it to aqueous phase it is going to start degrading and your polymer properties may change. So, the alternative to that is to sort of just avoid water completely in this synthesis process, if you notice here there is no water that is present throughout this process.

So, you do not have to worry about whatever that happens to the anhydride bonds which may get degraded in presence of water. So, as I said they degrade very rapidly in water and then polyanhydrides typically also have very low Tm so; that means, that they can

become liquid at a fairly low temperature. So, that helps in let us say if you are using a biomolecule and you do not really want to heat it to 100 degree Celsius. So, that helps because if you let us say heat protein 100 degree Celsius it is going to get denatured. So, its relatively milder conditions for your drug.

As I said if you have; if you have polymers that have higher Tm which some of the polyanhydrides can, then the drug stability becomes an important consideration. So, it is to use let us say small molecules in that case, but something like proteins and all you cannot really use at higher temperature, they will get denatured and there is really no purpose that they are going to serve in the long run.

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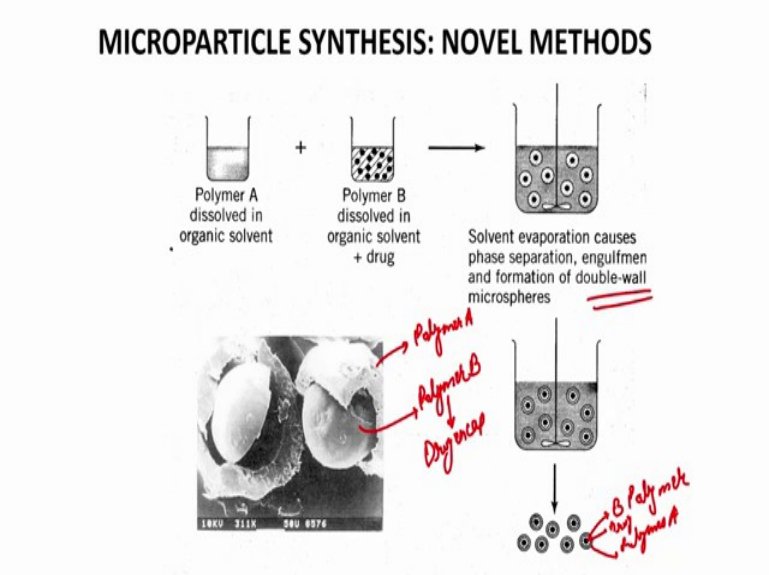

So, there are some novel methods as well that are used. So, in this case it is been shown that you can take polymer A and dissolve it in an organic solvent you can take polymer B dissolved in some organic solvent also containing drug, you can then mix them up and then have sort of a double layered polymeric particle where you have your polymer B inside which your drug is encapsulated and then outside you have polymer A.

So, now, you have two sort of layers of polymer that can help in encapsulation the drug in sort of double walled microspheres. So, if you do an SEM of that you see that double walled structures - first you have in this case this is your polymer A, this is your polymer B and then this polymer B will also contain drug inside.

So, you can have different variations to these particle synthesis methods and very easily have different sort of polymers and different sort of drugs have different release and different applications.

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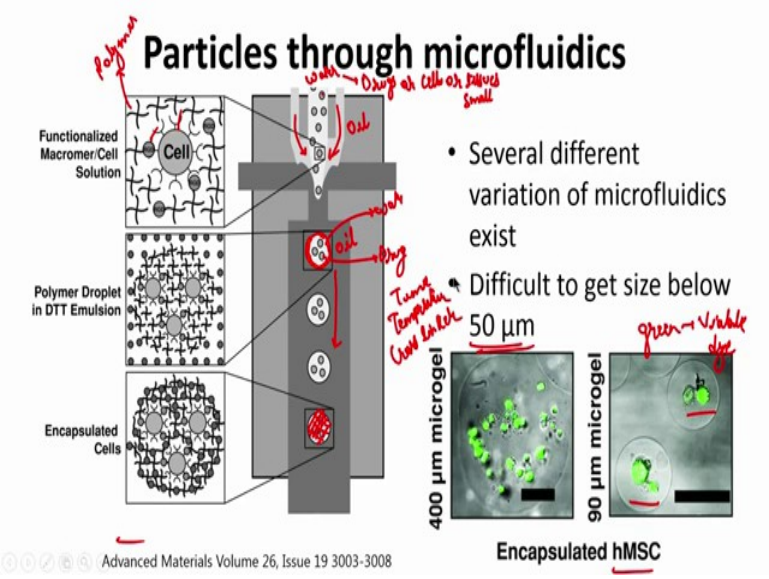

So, here is another example and this is a microfluidics based encapsulation. So, microfluidics is a big buzzword these days and getting more and more popular as the time goes on. So, what it is essentially you can have and this is just a model microfluidic channel I am showing you there are several variations to this that exist in the literature.

So, what you can have is you can have sort of a two way nozzles. So, on the outside you can have let us say an oil phase, inside you can have let us say a water phase which may contain your drug or your cells containing drugs or cells or tissues (small tissues that is) and so essentially if you zoom in here what you see is this - you have these polymer chains containing either the cell or the drug and then what you do is you come in with the oil phase with some surfactant. So, what will happen is this will pinch up as a droplet.

So, essentially a very similar concept with a double emulsion - this is also sort of an emulsion, but with single droplets at a time and so this is oil, inner is a water and then further you have your drug could be either small molecules or could be cells. And then as the time goes on this polymer starts to polymerize, this could be just with the time, this could be with temperature or this could be with some cross linker that might be present

in the oil phase and because of that by the time this thing exits this is all cross linked and whatever is inside gets encapsulated.

So, in this case they are showing here in this particular paper that they have done some live cell encapsulation in this case human mesenchymal stem cell and you get very nice viability- green is in this case is viable dye and here we see that all the cells are being labeled as green which means that they are all alive.

So, as I said there are several different variation of microfluidic that exists in the literature. However, they all suffer from one of the limitation which is its very difficult to get these droplets down below 50 micron. So, the particles will get are going to be 50 microns or higher. Some people have been able to show somewhere down to 10 microns, but then it is very difficult to get below that.

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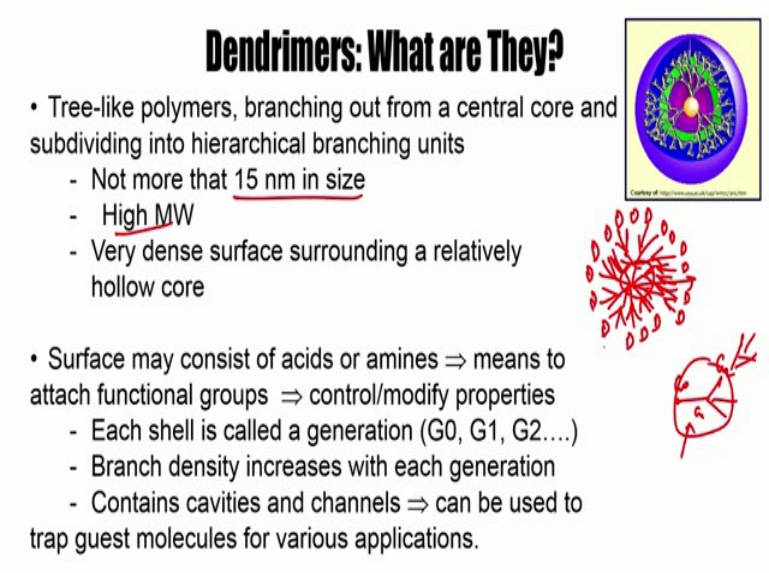

So, these were all the particles in these methods which involves some sort of emulsion based process or some other format the next we are going to talk about another class of particles which is called dendrimers and here is a cartoon of dendrimers and so what essentially they are is they are these tree like polymers which are branching out from a central core. So, you can have a central core and then from there will be sort of hierarchical branching out which can happen let us say you have one sort of reaction that happens on the central core.

And that results in this and whatever you attach to it you have another set of reaction that can happen to those and that will result in a structure like this and then similarly this can continue to go on. So, as you can see there is some sort of order to this, the inner you go the more space there is whereas, as you go out from the central core there is more and more cross linking that is happening and that results in kind of a very dense network of these branches.

And typically the dendrimers are not more than 15 nanometer in size they have a very high molecular weight, you even call them very high molecular weight polymers for that matter, but with a certain order and hierarchy and they have a very dense surface surrounding a relatively hollow core.

So, essentially this is relatively hollow compared to the outside and this is going to continue so and so forth. So, these surfaces may consist some acids or amine or other functional groups that you can use to attach different drugs. So, typically the drugs is covalently attached to it. So, you can then attach your drug D to all of these outside branches and because it is nano-size it has a very high surface area you get a very high drug encapsulation or drug conjugation on the surface and the way there is a defined as these are called generation.

So, G0 is the initial core, the first branching is essentially G1, the subsequent branching is G2 and so on and so forth. Typically these go on up to G6, G7 and because this sort of this hollow structure in the middle you can use this to also entrap bigger molecules within this structure. So, if you continue this reaction in presence of those molecules they will get entrapped within these structures as well. So, there can be entrapment as well as covalent conjugation on the surface.

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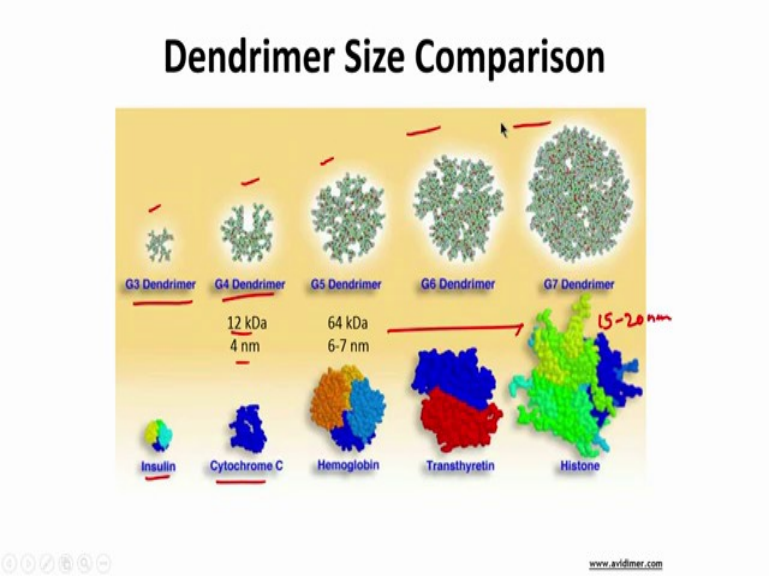

So, here is an example, so in terms of the size itself the sizes are typically small. So, G3 dendrimer is very similar to an insulin molecule, G4 dendrimer is very similar size to the cytochrome which is about 4 nanometer or 12 kDa and similarly the sizes go on up to 15 20 nanometer, but not really more than that. And this is just a pictorial representation of how each of them looks. So, we will stop here and we will continue our discussion on these particles in the next class.

Thank you.