Drug Delivery Principles and Engineering

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Lecture -18
Nano and Micro particles – I

Hello everyone, welcome to another lecture of Drug Delivery Engineering and principles. So far in this course we have discussed several things; initially we discussed pharmacokinetics, pharmacodynamics of the drugs, we discussed about pro drugs. And then, from there on we started talking about how can we then change this free drug delivery to something else so, that it gives us a very high sustained release as well as controlled delivery.

So, in that we have discussed, first of all, polymer drug conjugate, which is essentially adding the polymers to the drug which increases their size as well as prevent degradation. We have even talked about using some sort of a matrix so it could be a reservoir system. So, you have a big reservoir and then you have slow release. So, few drug through that either just by diffusion through a small pore or by an osmotically driven pressure that causes the release of this.

Then we have also talked about matrix based delivery. So, these could be non-erodible; that means, they will not degrade, but then the drug can slowly diffuse out from these systems. Once you implant this you will have to basically do a surgery to first put them in and then another surgery you take them out or you can change that by then making them bio-erodibles and what that does is, the implant will just a erodes and as it erodes the drug will come out. It could be a combination of both erosion and diffusion and in that way, you will only have to do one surgery because once you put it in, after a certain period of time which could be weeks or months depending on what type of implant it is, it will just degrade and go away.

Then we finally, discussed some sort of examples of these two matrix types of delivery using hydrogels. So, hydrogels can again be both either erodible or non erodible, but then depending on what you are using in terms of polymer, they might degrade or they might stay there forever. And then we discuss how hydrogels are being used for drug delivery, what is the concept there. So, this is a swelling based method and then also discuss some

of the mathematics behind how to figure out how much swelling ratio is there, how much the pore size is in a hydrogel. So, that helps us in defining what kind of drug to use and what drug is feasible as well as what will be the release rate of the drug.

So, now so, these were all macro devices more often than not we require surgery although in terms of hydrogels, we were talking about in situ cross linking, and that means that we do not have to do surgery we can directly inject, but for nearly all other types of applications we have to discussed, so far, and in terms of matrix, reservoir and all kinds of things. We are talking about some either small surgery or big surgery being performed to put these things in and in some cases also another surgery being performed to take them out.

So, today we are going to talk about another class of drug release devices and these are macro and nano devices; and very big, famous words these days and lots and lots of research are going on in terms of making microparticles, nanoparticles and then using them for clinical applications. And so, we will talk about in discuss this in quite a bit of detail as to what these things are and how they are being used for different applications.

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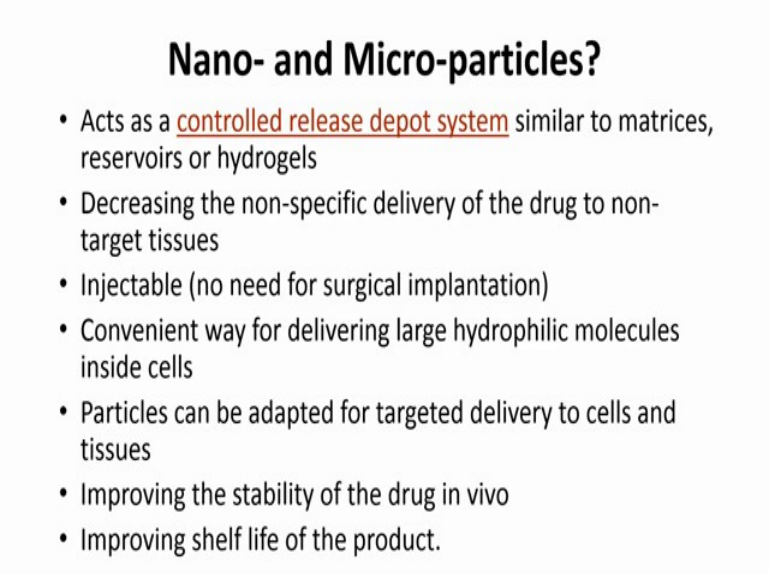

So let us start with the nano and microparticles. So, like what we have discussed in the past with all kinds of our initial systems as matrices and reservoirs, these are also control release depot systems.

Very similar to these matrices, reservoirs and hydrogels, they can take any of these forms, but now instead of having a big macro device, you have now split that into small devices. And what that allows you to do now is basically directly inject these devices into the body using some syringe - this is let us say 1 centimeter or even higher, but now that these are less than, let us say, 1 millimeter, we can use standard syringes which are having diameters in some micron ranges and directly injected into a system whereever we want to put them in.

So, this also allows you to decrease the nonspecific delivery of the drug to non-target tissues. So, let us say, if I want to deliver something to my brain, I cannot really put a device to my brain because a brain is a very sensitive organ and I do not want to damage it. So, maybe I was putting it under my skin somewhere and then hoping that the drug will then come out from this and diffuse and go into the brain. But now, with these injections, I can find a small pocket where I can inject without worrying about damage to the brain itself and so, that will basically mean that more of my drug is going to get release in the tissue that I want rather than they lying on the body to diffuse it or to take it to different organs.

As I said, the one of the biggest advantage is their injectable. So, there is really no need for surgical implantation. One of the biggest issue with this is the hospital visits and the patient compliance every time we talk about surgery, the patients are also worried about their lives and that will can be lots and lots of complications that may happen, anesthesia is involved and those can always be little tricky. And then there are the chances of an more and more infections because once your body is open from the environment, you can contract lots and lots of different types of infections. So, all of that can be sort of countered using these particles.

It is again a very convenient way to deliver things inside the cells. So far what we have been doing is, we have been relying on the drug to basically go and diffuse into the cell that is ok for small drugs which are fairly amphiphilic or hydrophobic, but for the drugs which are large and hydrophilic or maybe even charged, those drug molecules do not really diffuse into the cells. So, let us say if I want to make a device or a drug that is targeting the DNA of a cell, then the cell is a very good barrier - these lipid membranes that are represented on the cell, any kind of hydrophilic molecule will just be repelled away and it will not be able to enter the cell, but we will talk about how these nano- and

micro- particles can actually help us target this intracellular niches well if we want to target that.

And then, of course, they can we can also further target them. So, that what types of cells or what types of tissues, we want them to go to even though they might be systemically administered. Because they are small and they can go around and explore their way through different areas, you can have a situation where you can put a (ligand on them for extra targeting). Let us say, this is flowing in a blood vessel; let us say this is the blood vessel and your particles are flowing, let us say this is a healthy region, this is a healthy tissue and then this blood vessel is now traversing to let us say diseased tissue.

And maybe you do to the disease, there may be a some markers that are being expressed on to these endothelial cells which are not present here. So, what you can put what you can do is, you can put a subsequent ligand on these particles and since they are flowing they will explore and essentially use these ligands to bind to the receptors and they can hence impart more specificity. Because what will happen is more and more of these particles will accumulate at the disease site while they continue to flow through the healthy tissue.

So, that is another way that the these particles give you a lot more control and targeting, then let us say a big macro device. And then like the macro device, they can improve the stability of the drug in vivo of course, if there is enzymes that can degrade the drug, these particles at least till they are flowing in the blood, they will prevent this enzyme to get access to the drug. And only when the drug is released from the particle or when they reach the target site is these can act.

So, this gives you an additional stability for the drug molecule. And then it also improves the shelf life for the same reason- now this drug is not really liable to degrade due to various processes that might be present in your storage buffer or in storage conditions. So, these polymers sort of act as shield, so, till they are given and administer into the patient they might be able to increase the shelf life of the product.

So, let us say if a drug was very liable to degradation over time due to some particular contamination in your storage or due to some temperatures fluctuations, these polymers may increase the shelf life by any anything between 10 percent to 100 percent or just depends on the drug that you are using.

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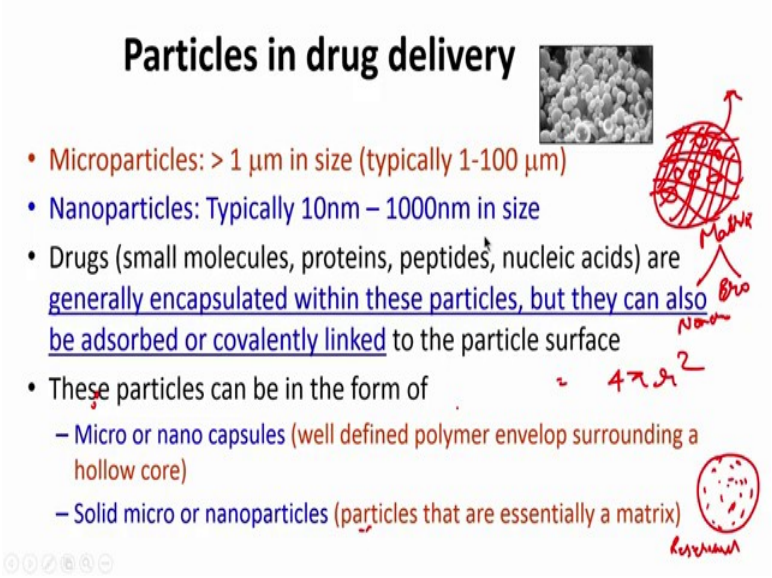

Let us further talk about particles in drug delivery. So, particles are fairly standard, these are some SEM images (scanning electron microscope images) the particles, which shows some polymeric particles of various sizes into this mixture.

So, let us define few things. So, microparticles are typically defined in the literature for a size greater than 1 micron in any of the dimensions, but they can be spherical they can be some other shape as well. But if the micro particle size is greater than 1 micron typically between 1 to 100 that is typically defined as a microparticle. Nanoparticles defined in the size range of anything between 10 nanometer to 1000 nanometers, again these are these are not standards- these are something that generally the field follows, but what you will find is even in the literature people may have a 2 micron particle and they may have refer to that is nanoparticle and vice versa they may have a 500 nanometer particle which they might refer to as a micro particle.

So, these definitions are bit fluidic, but this is what typically is being defined here. The drugs are typically small molecules- these could be proteins (which are fairly large), these could be nucleic acids, peptides, enzymes -they are typically encapsulated in these particles. But one thing that you will find different here compared to your matrices is they can also be adsorbed or covalently linked to the surface.

So, because what you have done now is, earlier you had a macro device, that had a certain surface area, which was fairly low when you compare the amount that can be

added here in the bulk volume in this large bulk volume versus something on the surface. The ratio was fairly low for the surface area, but now what you have done is you have now broken this down into several small small particles.

So, the amount of the drug that can be loaded on the surface has become quite significant, when you compare it to the amount of drug that can be put in the bulk volume. So, with the microparticles and nanoparticles, you now even have that capability that you can put things on surface and be still be able to load quite a lot of drug. As the size decreases, this surface area to volume ratio will increase.

So, let us say for a particle, what is the surface area? Let us say it is a spherical particle. So, we have surface area and we have volume. So, for spherical particle the volume is nothing, but

$V= 4\pi r^3/3$

What is surface area for a sphere? It is nothing, but

Surface Area = $4\pi r^2$

when I say that the surface area by volume will increase as the particle size goes down. So, let us do that.

Surface Area/Volume = $3/r$ this is for a spherical particle.

So, as the r increases, the ratio decreases and as the r decreases, this ratio increases. So, eventually when you shift from this to this and further down to nanoparticles- let us say these are micro and then you go down further to nano what you will find is that the r is constantly decreasing as you are going there and your surface area to volume ratio is increasing. So, now, you can load more drug inside on the surface, then in the volume at a certain size range for a certain application. And then of course, these particles can be in form of as I said they can take various forms, they can either be a matrix, or reservoirs so, you can have sort of particles that are completely hollow - you can load your drug in them. So, they are sort of a mimic for reservoir system or you can have a particle which is completely filled with polymer and then that drug is essentially just encapsulated in between these polymer chains. So, this is sort of a matrix system and then, as I said, matrix systems can both be erodible or non erodible.

So, these particles can also have the same form, they can either degrade and release the drug or the drug just has to diffuse out from these polymer matrices. So, all of those are fairly feasible the same applications, and the same sort of kinetics are applied just the surface area and the volume is changed.

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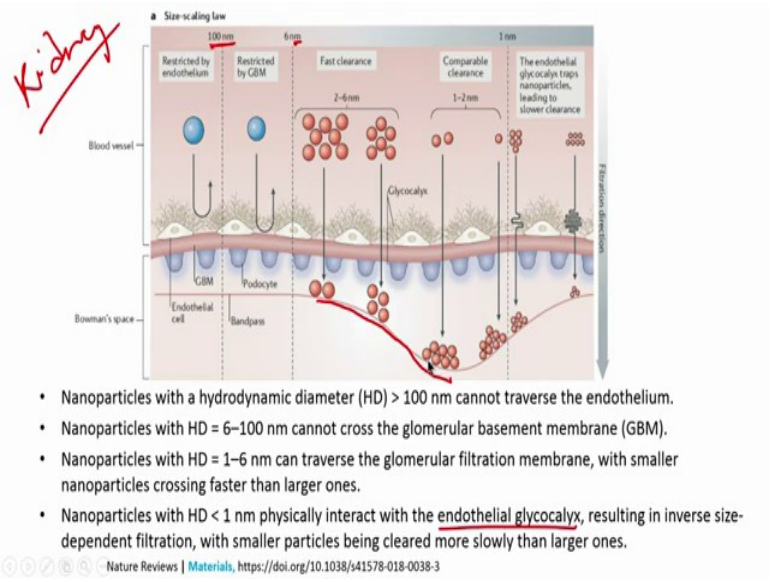

So some more terms, definitions here- what we are looking at, is the filtration through kidney; so, this is the kidney that is zoomed in. And what we are looking at here is the interface between the blood vessels and the kidney cells. So, we have discussed this briefly earlier, but now we are trying to find out what will give us an enhanced circulation of these particles, in vivo. So, if I have a particle which is, let us say, in 100 nanometer size range right what will happen is the endothelium itself is tight enough that these particles cannot go into the kidney cells or kidney tissue.

So, these endothelial cells and whatever the surface proteins and glycoproteins that are present will be able to block that. Now as your size decreases from 100 nanometer down to 10 nanometer, this blocking will still happen but will continue to reduce. Once you go down below 6 nanometer where these particles are now between 2 to 6 nanometer, they can just pass through that and again the smaller the particles are, more the permeability.

So, what you will find is in they will start going in the kidney tissue in higher numbers as it goes down. However, what happens is at a certain size range let us say below 1 nanometer or around 1 to 2 nanometer what will happen is, now the sizes are so small

that they might start interacting with these glycoprotein surface. So, if I zoom into this is essentially nothing, but a cell surface with lots and lots of proteins and sugar moieties that are present on the cell membrane.

So, earlier what was happening if I have particle which is fairly big compared to all these, this particle was not even going in there and will just go out from some surrounding area. But now that the particle has decreased and it did become a size which can actually go into these glycocalyx or glycoproteins, what will happen is the particle that starts going in there gets entrapped, then has to go through a long tortuous route before it can go out. So, because of that now their residence time or at least the filtration through kidney has become lower and lower.

So, this happens to certain extent and then there will be a time when this size becomes so small that even if it is interacts with it still goes right through. So, what you find is the filtration by the kidney essentially act as a band pass, where anything above 6 nanometer is not filtered at all. Whereas, as you decrease the size from 6 nanometer down to 1 nanometer more and more particles get cleared. But if you go further down, then it gives much more resistance as well. So, that is just something to understand and remember.

So, again and this is just describing what I just said. So, nanoparticles with the hydrodynamic diameter of greater than 100 cannot traverse to the endothelium, in between 6-10 nanometer, they cannot cross this basement membrane, which is fairly impermeable to any of these particles. Once you get down between 1 and 6 nanometer, they can go through this basement membrane. The basement membrane is nothing, but a membrane below the endothelial cells and the smaller they are the faster they will go up to one nanometer or so. And then the nanoparticles with the hydrodynamic diameter even less than 1 nanometer will then interact with this endothelial glycocalyx and that would mean that once they are in that size range in the similar pore size. They will interact more they will have a longer path, they will then have to travel and that will cause these smaller particles to have a larger residence in the blood vessel in this region, then let us say a smaller particle.

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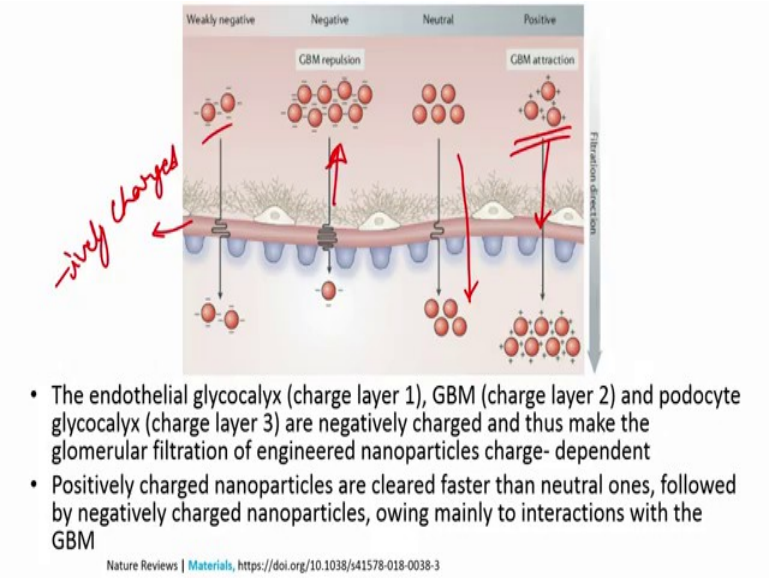

And let us talk about how the charge plays a role. Let us say now the particles can also be charged they are still moving around. So, the charge could be either negative, neutral, or positive. So, what happens in all three conditions? So, as we see here, if it is fairly neutral, there is really not a whole lot of interaction that is happening. So, it may have a certain sort of a flow through that, but the basement membrane itself is negatively charged. So, if you have positively charged particles, because of the electrostatic interaction more and more will come and they will have a higher flow through that.

Weakly negative charge also does not really play a whole lot, but if it is highly negatively charged, they will be repelled by the basement membrane and they will have a higher circulation time. So, that is what is written here. So, essentially positive charge nanoparticles are cleared faster than the neutral ones, followed by the negative charged particles because of the basement membrane, which is negatively charged and that is why you see the effect that I just described. I will stop right here and we will continue in the next class.

Thank you.