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

Lecture - 10
Controlled Release Reservoir System – I

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

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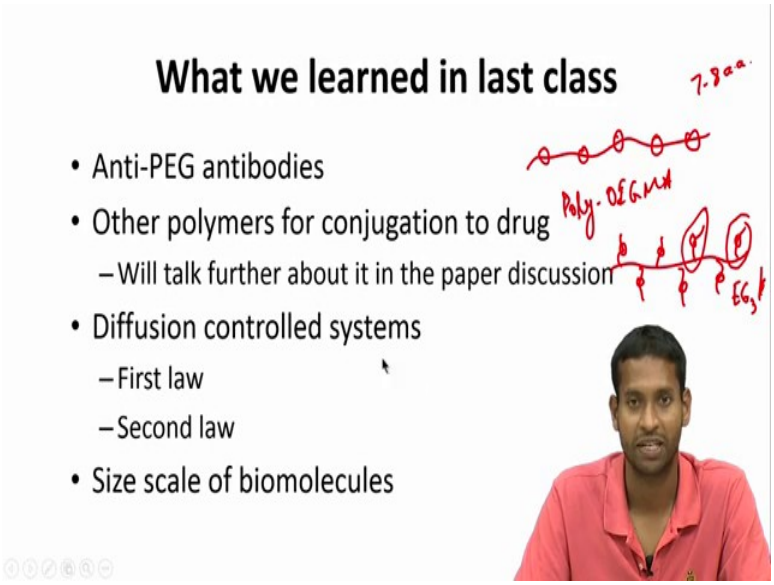

So, let us do a quick recap of what we did in the last class. So, in the last class we had talked about polymeric drug conjugates and then we further discussed that the PEGylation is one of the most widely used strategies for polymeric conjugates. It increases the residence time, let us your drug to be more soluble, it makes it to be more effective and control release as well. But then what we discussed is now that the PEG is very widely used, not only with the polymeric conjugates, but with also some cosmetic products like creams and eye drops, people are now starting to report Anti PEG antibodies against this PEG polymer.

So, because of these antibodies now being produced there is a risk that people may already have these antibodies and once you inject whatever you trying to deliver, the presence of these antibodies will cause a rapid clearance. So, the job the antibodies essentially to bind and let the immune response that this is something foreign and that is

also going to cause severe reaction and inflammation. So, it could be actually quite dangerous for people to get these PEG products if they have PEG antibodies in them.

Then we discussed that what are the other polymers that we can use as an alternative to PEG for conjugation to drugs. So, even though as I said PEG was most widely used, there were other research simultaneously that was going on other polymers that could be used. So, we discussed few of those, one of the major ones we discussed was poly oegma which is a very similar polymer to PEG, but instead of a long chain PEG it is a long backbone on which small PEG units are then attached.

So, essentially PEG, if I say this is PEG, with lots of ether bonds, in case of this poly oegma, I have a polymer backbone with PEG chains, small PEG chains attached. The reason why this has not generated antibodies is still not very clear. There are reports saying that because these units are so small, they probably not been able to bind to the receptors to which a long PEG chain molecule can bind.

So, typically the receptors in the immune system that binds to any kind of antigens require somewhere around 7 to 8 amino acid long chains, or in other terms we are talking about at least 700 to 800 Daltons, but with PEG that small unit that we have here. So, if you remember we were talking about EG 3 or EG 9 these are fairly small and they would not be able to bind to this receptor which requires at least 7 to 9 amino acids. So, maybe that is the reason and the other reason could be that we have not explored them enough.

So, maybe like PEG once this gets explored more, we may have a lot more reports some antibodies coming against team in this polymer so, we will see only time will tell us. So, other thing we talked about was diffusion control systems. So, we discussed this paper, so, this is already discussed. Other thing we talked about is diffusion controlled systems which basically we first defined first laws. So, the first law what was the first law? The first law was defining the diffusion in the random walk. So, the diffusive flux is related to the diffusion coefficient as well as the change in concentration.

Then we talked about the second law which again is just a mass conservation. So, for a given volume you can do a mass conservation, you can find out what are the term what are the concentrations that are going in all x y and z direction and then the similarly what are the concentration of that particular molecule going out in x y and z direction. And if

there is any generation then you can add that term to this and if you do a mass balance this should give you whatever is accumulating in that particular volume.

And then towards the end we discussed very briefly as to what are the different size scales of these biomolecules, we found that proteins are fairly large molecules from 1 nanometer to 10 nanometers, even though their molecular weight may go quite high. So, 5 kilo Dalton do let us say 5000 kilo Dalton, the molecular weight is not going to change a whole lot, their radius is not going to change a whole lot they will only vary from 1 to 5 nanometer, because there is a cube root relationship.

And then we also talked about what is the intermolecular distance for a given concentration of a solute. So, we found out that at least for proteins at very high concentrations you will find that the intermolecular distance is actually lesser than the size of the protein itself. So, it is not even physically possible to have proteins at that high concentration they will just precipitate out, or would not go into the solution. So, we are going to continue our discussion on matrix devices and other systems that we can use to deliver drugs more efficiently.

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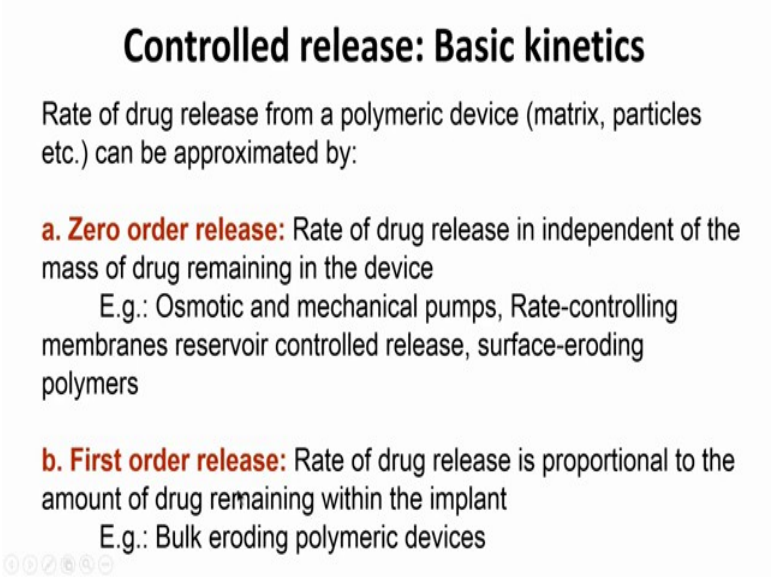

So, first thing we are going to talk about is some controlled release. So, let us do some basic kinetics. So, this is again going to be very similar to what we already discussed in terms of elimination. So, in terms of elimination we said that kidney eliminates things or

the liver eliminates thing and then this zero order, first order, elimination kinetics which basically defines how the solute molecules is able to eliminate from the system.

So, in this case what we will discuss is how instead of elimination now we are saying how whatever devices we are using, how they are going to release the drugs into the system. So, like the elimination kinetics this can also be zero order release and as the name suggests zero order essentially that the rate of release is independent of what is the concentration of drug within your device.

So, your concentration could be x, could be 10 x, could be 100 x, regardless of that whatever the drug is coming out from the device is going to be fairly constant. So, a lot of examples for these there are osmotic and mechanical pumps very widely used and there are rate controlling membranes and reservoir systems and also surface eroding polymers which are large enough also sure zero order release and we will talk more about these as we go along.

And then they can also be first order release, which is again quite commonly seen as well. So, in this one the date of release is proportional to the amount of drug there is remaining within the implant. So, if the implant is containing 2x it will have a higher release rate then an implant that is only containing x amount of drug. So, any bulk eroding polymers or even diffusion control polymers will show somewhat first order release.

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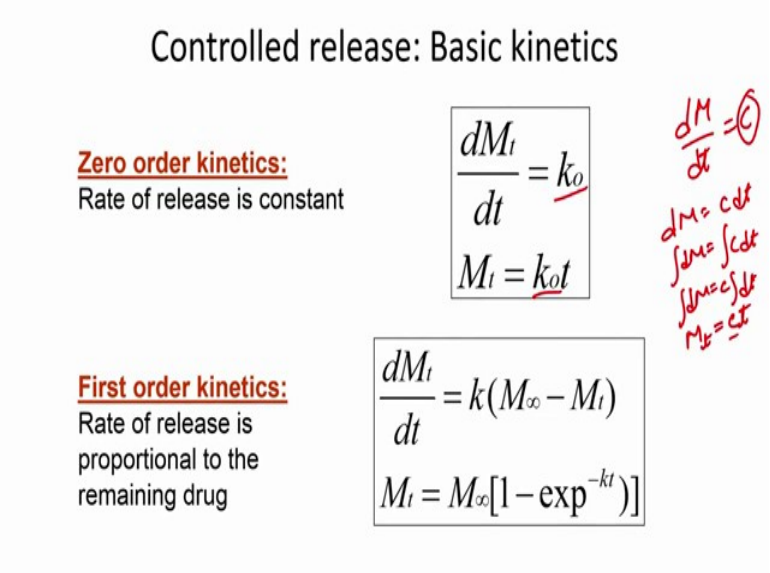

So, some basic kinetics I mean this is again very well understood. So, if you have zero order kinetics we are saying the rate of release, so, let us say that is dM by dt is going to be constant. So, let us say that constant in this case is k0 so, you just need to integrate that.

$$\frac{dM_t}{dt} = k_o$$

$$M_t = k_o t$$

So, you can just do dM is equal to cdt and if you integrate both sides you will get c is constant. So, you can take c out and essentially it will just become at any time t it is equal to ct and in this case the c is replaced by k0. Then you have first order kinetics again fairly standard in this case as well. So, in this case what we are saying is at any time t.

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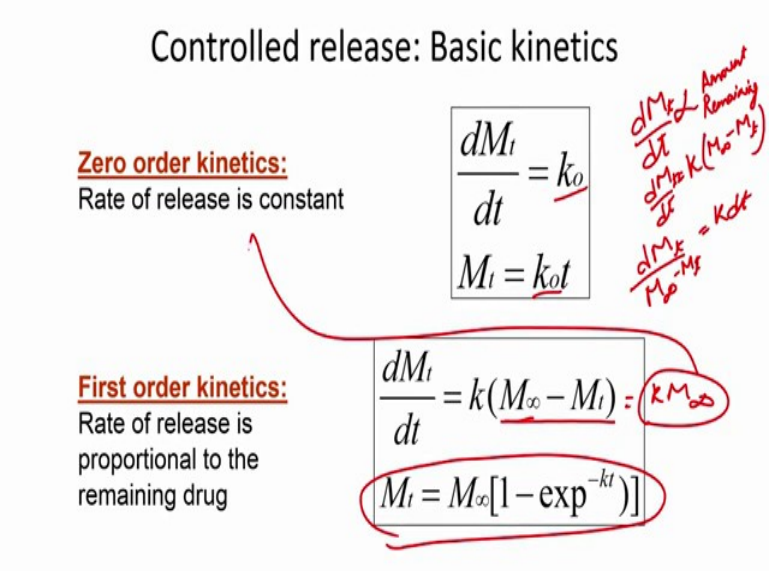

So, if I have to represent this, we are saying that at any time t, dM by dt will be equal to will be proportional to the amount remaining. So, if I remove the proportionality constant so, it will be dM by dt is equal to again k in the amount remaining and what is the amount remaining.

So, we know what is the initial amount that is there, let us say that is M infinity the amount that gets released at the time infinity whatever the drug was loaded and then the amount that is already released at the time. So, if I am saying this is a time t, then whatever is remaining is the initial minus whatever is released.

$$\frac{dM_t}{dt} = k(M_\infty - M_t)$$

Now if I have to integrate this I can easily integrate this by separation of variables.

$$M_t = M_\infty[1 - \exp^{-kt}]$$

So, and this will essentially give me the concentration of the mass released at any time point.

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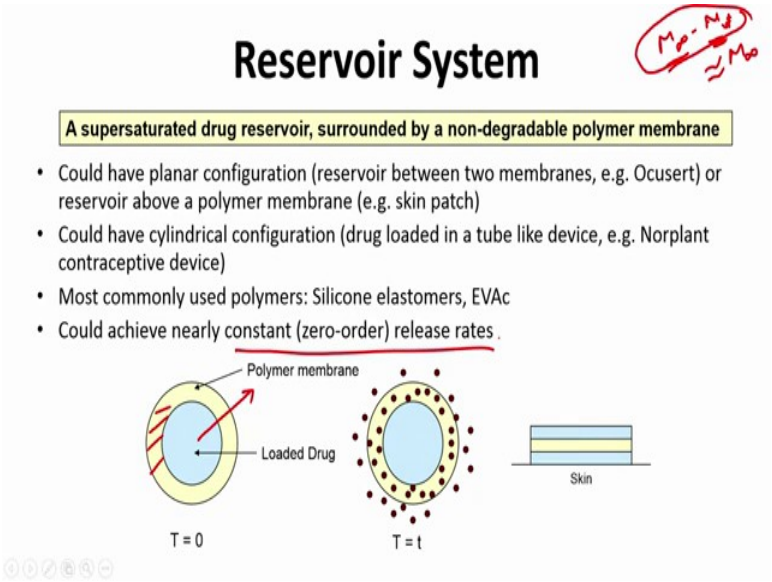

So, let us talk about reservoir systems now that we have that out of the way. So, what are reservoir systems, reservoir systems are essentially a supersaturated drug reservoir. So, typically when you are talking about these implants and these reservoirs you are loading lots and lots of drug in these systems.

And so, your reservoir will then contain quite a lot of your drug and so, you can consider the drug in the reservoir to be very high. So, even if at initial times at least or for quite a bit of time whatever amount is releasing is still negligible to whatever amount is

remaining. So, in that case what we are saying is this M infinity minus Mt for most of the initial times this Mt is still with very low compared to M infinity.

So, this can be approximated as M infinity itself and so, that is why and this rate of change is as we saw from the previous slide that this essentially is dM by dt is proportional to this and as we are saying that this is equal to M infinity itself that would mean that this is also constant. So, this becomes a zero order kinetics.

So, these can have various kinds of confirmation, typically you have a reservoir, which then surrounded by some kind of a polymeric membrane or could be some other membrane as well and then these typically can have any confirmation you want could have a planar configuration, could have a spherical configuration.

So, you the skin patch is that a good example of this, you have a reservoir kind of sandwiched between 2 membranes one is; obviously, a non permeable and another semi permeable that is attached to the skin and then the drugs can release from this reservoir through this membrane into the skin. Or these could have other cylindrical configuration depending on what you want to release, at what rate and we will talk about some of the examples as well.

So, essentially whether it is spherical or whether it is skin patch it has to be some sort of a membrane through which this drug will diffuse out as shown in this diagram. Some of the most commonly used polymers for this membrane are silicone and EVAc as I just described here and you will get a constant zero order release rates through this system.

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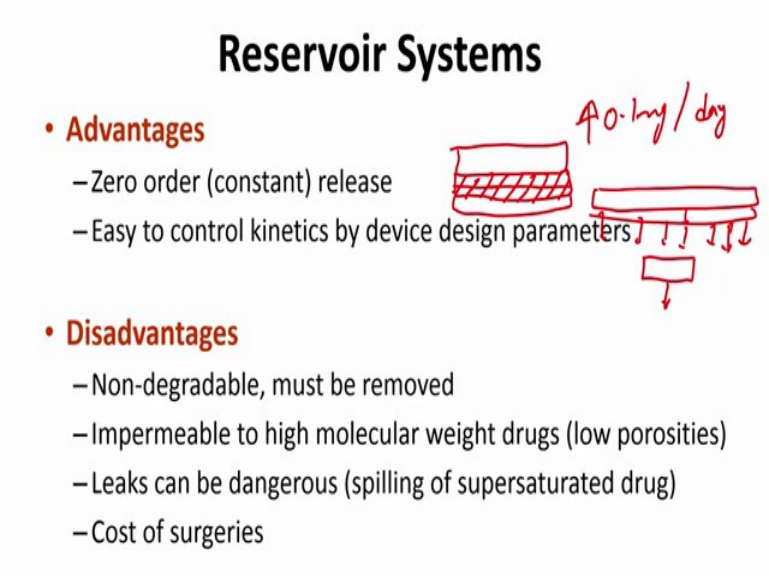

So, what are some of the advantages that these provide; obviously, one is that it gives you a zero order system, what are the other advantages it is very easy to control the kinetics of the release by just changing the design parameters.

So, let us say if a system gives me, if let us say this is a reservoir and this is the polymeric membrane and let us say I am getting a release rate of 0.1 milligram drug per day and now I want to change the system. So, that this increases, all I have to do is just reduce the thickness of this polymeric membrane. Once I reduce thickness of this polymeric membrane this rate will go up and vice versa if I want to decrease this rate then all I have to do is just increase the polymeric membrane, but I can also change the design itself. So, I can make this smaller.

So, now there is a less area through which the drug is diffusing out. So, that will reduce the release rate or I can make this much larger with the same amount of drug and in that case now there is a lot more area through which the drug can go out into the system. And so, that is going to increase the release rate of the drug. So, it gives you lot of control in terms of design parameters, what are some of the disadvantages of this system?

So, one disadvantage is non degradable. So, if I am implanting this in the body, you will have to get another surgery to either remove it or it will always be in your body which may cause some adverse effect. Typically, these systems which are diffusing through these membranes, they only really work for low molecular weight drugs, if you have

high molecular weight drugs, something in 100 kilo Daltons or 1000 kilo Daltons, these porosity is through these polymeric membranes and not good so, you cannot drug deliver very high molecular weight drugs through the system. Although there have been lots of technologies that have developed to make this reservoir systems compatible with that and we will talk about that in next couple of slides.

Leaks can be very dangerous. So, let us say now I have an implant that is implanted under my skin, in my arm what if due to some reason may be due to some accident or maybe just the mechanical properties of the device itself, there is a crack in the device. Now what will happen is, all the drug is going to come out immediately which will cause this supersaturated drug to now flood the system and as we know most of the drugs have certain toxicity in certain range and it is kind of conceivable that if all the reservoir comes out immediately. Then the toxicity range will be very easily breached and so, leaks can be very dangerous it could be toxic could even cause death.

And then of course, unless it is a skin patch if you are implanting this then the surgical cost also becomes quite significant you will have to go to hospitals, the medical practitioner will have to give you some anesthesia and then they will have to perform surgery in sterile environment. So, all of those costs add up and not to mention it is fairly invasive e at that point of time.

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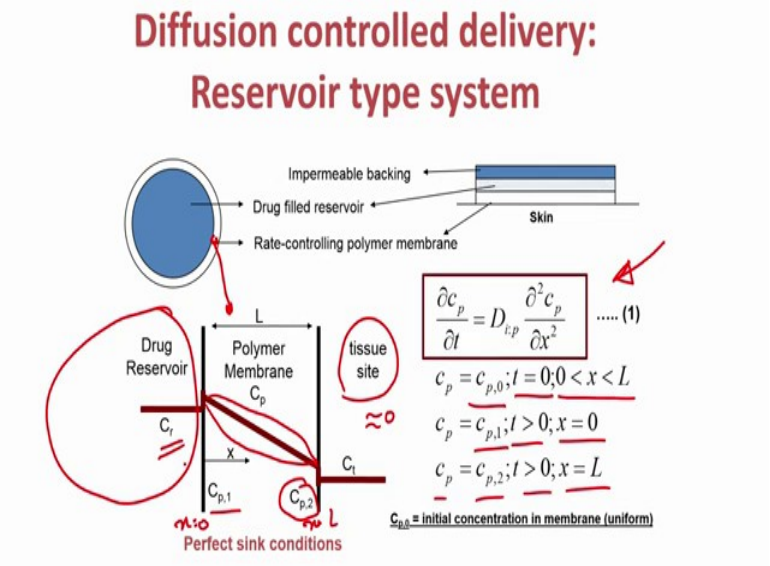

So, let us talk about some of the kinetics here. So, let us start with the reservoir type system. This is essentially what we described in the previous slide and so, what you can do is, you can set up your using your fixed loss you can set up the diffusion kinetics here. So, let us say this is the drug reservoir with a concentration Cr, this polymeric membrane has been zoomed in here and so, what you are looking at is, because now there is a higher concentration of drug here and this we can consider say tissue. And let us assume that tissue concentration is very low compared to the concentration in the reservoir which is how the system is designed anyways.

So, we can almost assume it to be 0. So, there will be some sort of concentration gradient, it may not be linear, it may be some other form as well it could be something like this or something like this, but there will be some concentration gradient going from here to here and because of that we can now use the diffusion equations to do that. So, let us say at the time 0, the concentration in the polymer membrane is Cp. Why Cp different from Cr and that is because it is a different sort of a network this is kind of a reservoir the solubility in the polymeric membrane of the drug will also define that Cp is different from Cr. And so, now, let us say so, what will be my boundary condition. So, again using the Fick's law equation we have thus now we are defining the boundary condition.

So, at time t equal to 0, I am saying that the devices form the devices enough time before it is used in the patient that the concentration in the polymeric membrane across the whole polymeric membrane is Cp. So, this is what it is said here.

$$c_p = c_{p,0}; t = 0; 0 < x < L$$
$$c_p = c_{p,1}; t > 0; x = 0$$
$$c_p = c_{p,2}; t > 0; x = L$$

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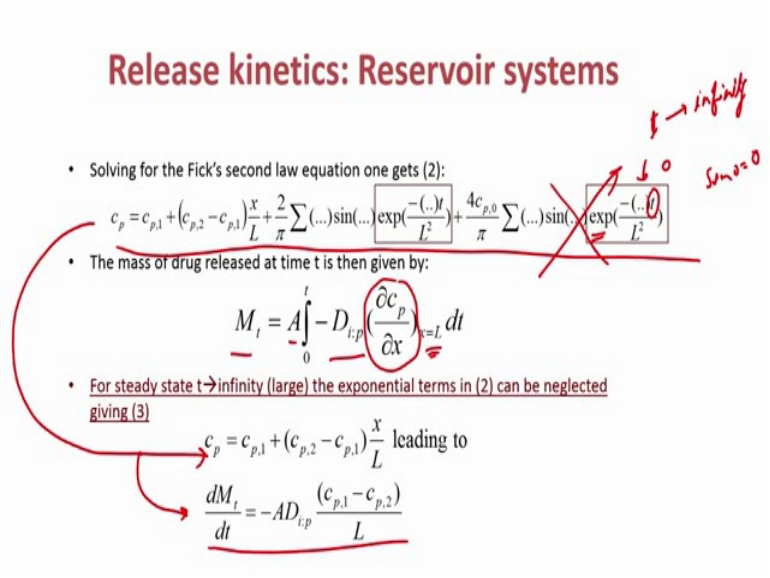

So, these are my now my initial conditions set up I can go ahead and solve this using various numerical methods and what I get is a equation which look which is relatively long solution and looks like this, but if you look closely here you have exponential terms that have a minus t in the exponent. So, what will happen, when this t is very large. So, at t reaching infinity you can essentially neglect these terms. So, because this is going to go to 0 and then sin 0 will be 0. So, all of these terms can be neglected, which are growing exponentially.

And so, then what you are left with is essentially a simplified equation, at the same time we know that the mass of the drug released will be what, will be area through which it is coming out the diffusion coefficient and the rate of change at any distance x and this will be in this case at the distance L, because that is where it is exiting the system and going into the tissue. So, once we do that, this top equation simplifies to this and then you can then calculate dM by dt from here, which comes out to be very simple equation here; obviously, this has some assumptions the actual rate will be different.

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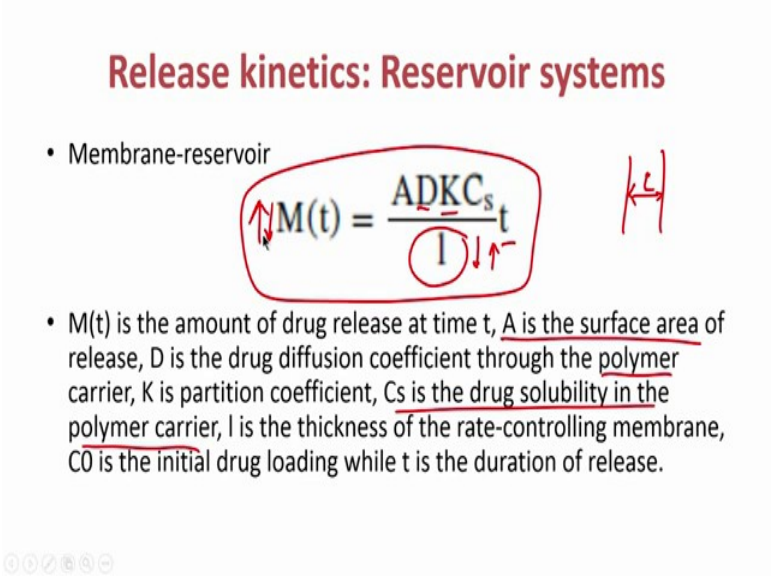

And essentially if you integrate this you get the mass released at time t, the total mass released at time t is equivalent to the area the in the surface area through which is releasing the diffusion coefficient of the drug itself in that particular solvent through the polymeric carrier. The partition coefficient of the drug so, if the drug is hydrophobic or hydrophilic it may want to stay in one of the other system.

So, the partition coefficient also comes in and then the solubility of the drug in the polymeric carrier is also there, time t is obvious and L is the thickness. So, if this is my polymeric membrane and this is L and so, in this case I get a equation like this. So, if I have to now change my release rate you can clearly see that if I reduce L my Mt will go up and if I increase L my Mt will go down. So, this is very easy to do with these reservoir type systems.

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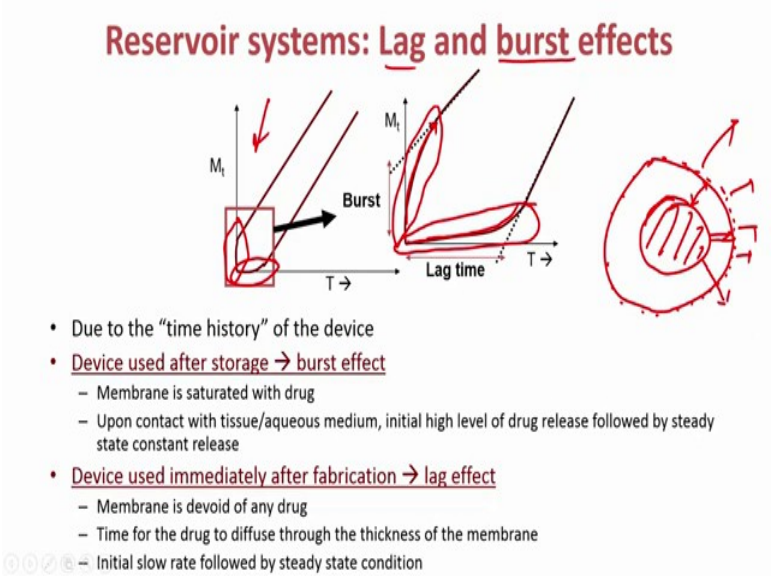

So, now I am going to define couple of other terms that are very widely used in the literature and associated with any kind of release matrix and also including reservoir systems, these are lag and burst effects. And what essentially are these is, if you actually do the kinetics the release of an actual reservoir body into a system. What you will find that, you will see some sort of an initial burst or an initial lag that will happen. So, if you zoom into this particular region you will find that there is some initial very fast rate of the drug needs and then it becomes stabilized and follow whatever kinetics zero order or some other order that you were hoping and similarly in some other cases you will see that this is actually reduced at the time and then it picks up.

So, why is that happening can you think of a reason of why this will be happening, I will give you a moment to think about it. So, this is happening because the device has a time history to it. So, maybe the device was formed a year ago and it is waiting for the patient to use it or maybe the device was just formed and is immediately used in the patient. And so, what will happen here is, if the device has been stored for quite a bit of time. So, if I draw that thing again with the reservoir here and a polymeric membrane here now lots of the drug is diffused and come right to the edge of this polymeric membrane.

So, now the moment you put it into a body or into a media all of this drug comes out immediately, that is why you see lot of drug coming out at the initial time point and then eventually it is going to start diffusing, defined by the equation that we just did. So, then

it will eventually follow this straight line or a zero order release kinetics. So, that is the reason for the burst and then as you can now imagine what is the reason for the lag.

So, what will happen if I use the device immediately after formation, at that point, all the drug is here the drug does not have time to diffuse into this polymeric matrix. So, if I used it immediately after the formation or the fabrication of the device, the membrane is devoid of any drug. So, it will take some time for the drug to come from here come to the edge and then diffuse out of the system and because of that you will have a lag effect. So, this is initially the time the drug is taking to come out and then eventually when the steady state is reached it is going to follow us zero order kinetics.

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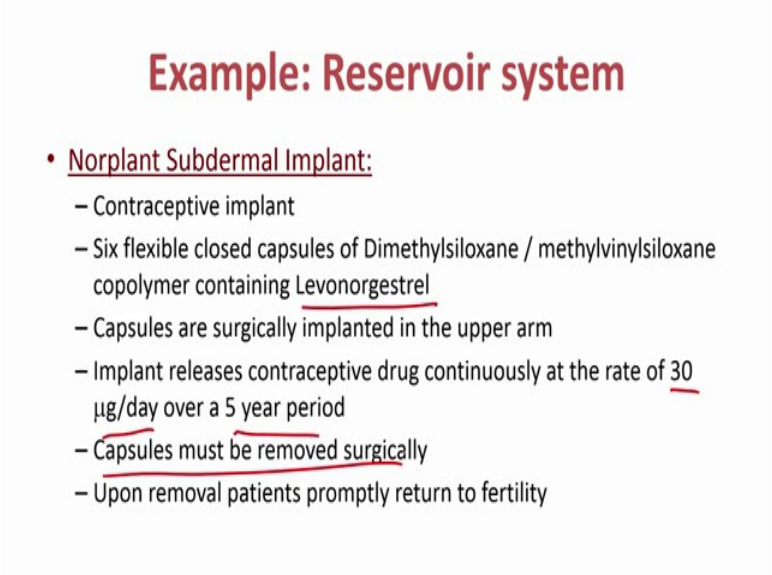

So, I will give you 1 or 2 examples of the reservoir system. So, one example that is very widely used is a Norplant subdermal implant. So, it is a contraceptive implant essentially to prevent pregnancies and what it contains is the 6 flexible closed capsules of a polymer which is dimethylsiloxane and then the drug that is contained there is this. These capsules are then surgically implanted in the upper arm so, somewhere in the upper arm of the patient or the person that you want to implant this in and what it does is this implant releases this drug levonorgestrel at a constant rate of 30 micrograms per day for over a period of 5 years.

So, if you want no pregnancies to happen instead of taking tablet us daily or monthly you can just put this implant and this will essentially ensure that the pregnancies are not

happening for at least 5 years. And of course, if you do change your mind you can always go back and take the implant out, once you take the implant out, whatever drug is in the system is going to eventually clear out within a day or 2 and that will not prevent pregnancies anymore. The issue of course, is then you will have to do surgery and also remove them surgically whenever you want to return to fertility.

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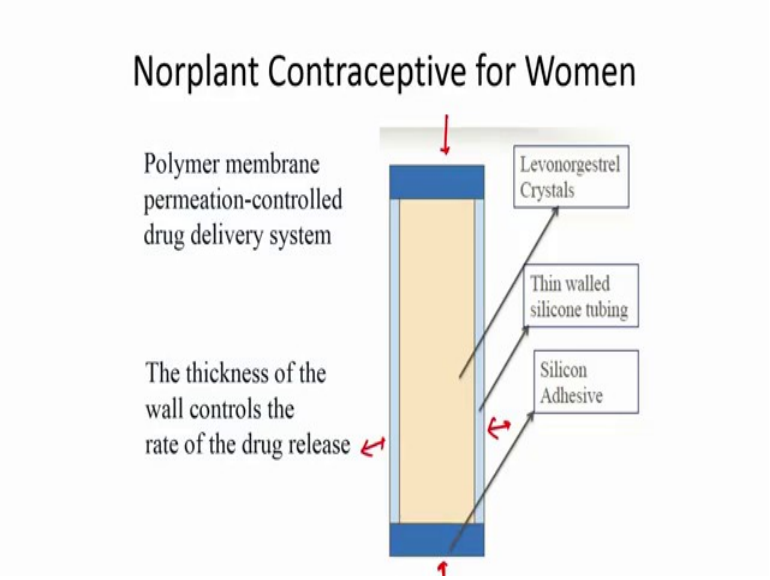

So, here is sort of the structure of the device. So, you have this drug loaded in this implant and you have a seal on both sides which is a kind of a silicone adhesive to make sure that the drug is not leaking and then these side walls the cylindrical shaped side walls are essentially what causes the diffusion of this drug, which is very slow diffusion it is a set 30 microgram per ml per day and that is how this drug is constantly released ok. So, will stop right here, we will continue in the next class.

Thank you for your attention.