Drug Delivery Principles and Engineering
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Lecture - 11
Controlled Release Reservoir Systems and Non erodible Systems

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

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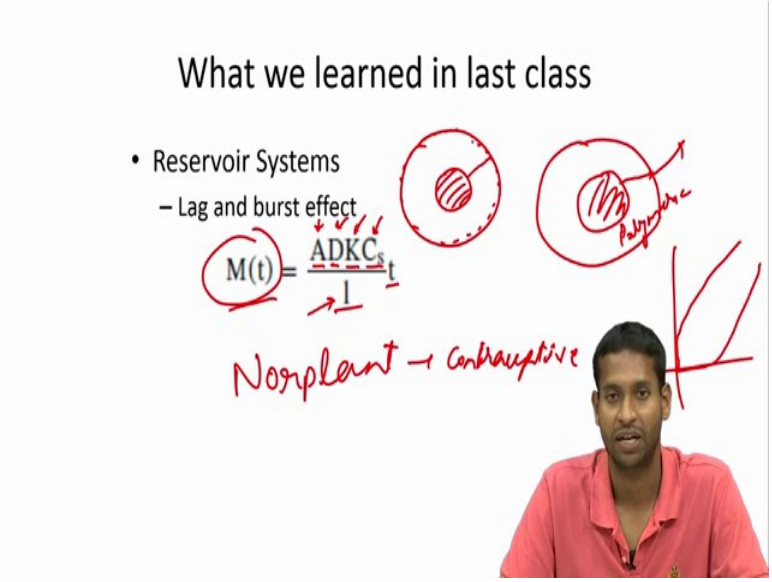

In the last class, we discussed reservoir type systems. So, these are again diffusion control systems which can allow you to get release of the drug over long durations as well as at the zero order kinetics and then we also talked about what is lag in the burst effect.

So, what is lag and burst effect? So, essentially in diffusion control systems if you have devices that are just manufactured and then all the drug is situated in the core whereas, the polymeric membrane currently has no drug. So, if you implanted immediately what will happen is, the drug will take time from here to here and before it can be release out in the system there is a lag that you will see before you get a concentration like this.

And vice versa the burst effect, if this device is already manufactured for quite a bit of time, then what will happen is the drug is actually diffused and deposited right at the

edges of this device. So, as soon as it comes in contact with the media lot of drug immediately comes out and then you have a release rate at whatever there is release of that particular drug is so, that is lag and burst effect.

Next thing we discussed was what are the sort of kinetics for which drug is releasing out, so; obviously, there was a big equation that we then made an assumption for t for longer durations and what we found is the rate of release of the drug is equal to the area through which it is coming out, the different coefficient of the drug the particle coefficient of the drug, with the polymeric membrane, the solubility in the polymeric membrane and what time point are you looking at as well as the thickness of the membrane.

So, it is very easy to change the release at any time t by changing either the area of the device itself or changing the thickness of the membrane that you are working with. Of course, if you change the drug itself, it will have a different kinetics because this D and K will change as well as Cs. So, all of that has to be considered ok.

So, we are going to continue this discussion and then we also discussed a couple of example of example of this which was the Norplant. Norplant device is a contraceptive implant that used this, but again as I discussed it has some advantages and disadvantages, it requires surgery as well as if there are leaks it can be fairly dangerous. So, there are other variants to this as well and so, another variant to this is reservoirs with the orifice.

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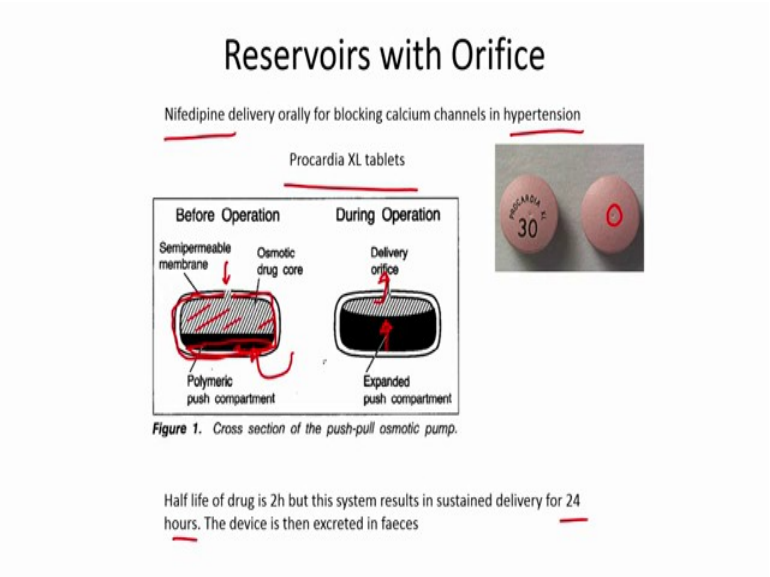

So, what that allows you well let me just describe you what this is. So, an example to this is Procardia tablets and these are just some oral tablets like any standard tablets, that you guys take, but instead of being a standard tablet what it is? It is some sort of a reservoir system and the drug that is being given here is Nifedipine, which is used to block calcium channels for patients suffering with hypertension. And so, this is how it looks as I said this is a fairly standard tablet and the key thing here is this hole that is present on the tablet.

And so, what will happen now is, there is some sort of a laser drilled hole which allows the drug to slowly diffuse out it is a very tiny hole in nanometer, 1 to 10 nanometer range depending on what drug it is. So, that allows you to have a very slow diffusion of the drug out and what is the driving force for the drug to come out? It is essentially osmotic driven.

So, it is a push pull osmotic pump and so, what it is, is before operation the drug itself, in this case this tablet does not dissolve like that like that unlike the other tablet us that you guys use. So, in this case this is a hard surface which will not dissolve in your stomach, but as I said there is a very tiny hole here and the drug is of course, loaded into the system and then there is a polymeric push compartment which has a very high osmotic gradient.

So, what will happen is, the solvent from the surrounding, once it comes in contact with fluid in your stomach and the gut, the solvent will tend to go in because of osmosis, because there is a higher salt gradient here compared to outside. Now, because this is going in what will happen is, this polymeric push compartment will start to expand and start to push the drug which is loaded in this reservoir. Now, this drug; obviously, can take certain pressure, but then after that it starts to slowly come out from this hole that was laser drilled in it.

So, that basically is a mechanism it is essentially osmotically governed it is still a reservoir system and that gives you a fairly smooth release rate. What it does is instead of this drug half life which is for 2 hours. So, if you take a tablet which immediately dissolves in your stomach and whatever gets absorbed. This will only have a half life over 2 hours, but this can allow you somewhat to increase that half life to 24 hours.

It prevents you from any kind of surgeries because this is again just a tablet that you are taking up, which gets excreted out through faeces and so, there is no surgery and the leaks are not typically that dangerous, because it is anyways in a flesh out system. So, even though it may cause toxicity it is not as dangerous is the Norplant implant which is already in the skin. So, this is one of the alternative to that.

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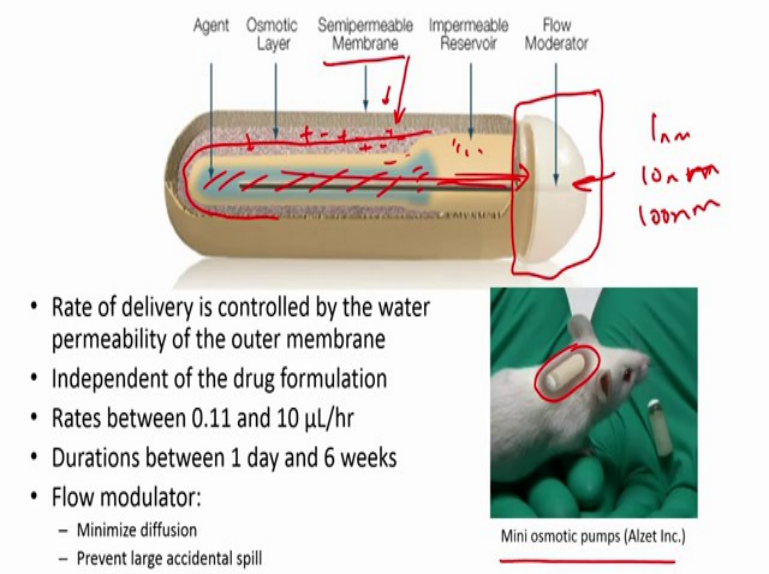

Another example here is these Alzet mini osmotic pumps and what are these. This is kind of a picture to that. This is just for a size scale, very widely used actually in research for animal experiments. And this is really a size of capsule this is just to give you some sort of an idea of how big this is, pretty much like less than half of the finger and what it contains? It contains several components.

So, like the previous system it has a semi permeable membrane outside on the outer core, then you have an osmotic layer containing very high concentration of salts. So, this is highly charged and highly filled with lots and lots of ions and then on the inner core you have your agent filled up into a reservoir with a hole through all of this. This is an impermeable reservoir, but this is somewhat flexible so, it can push the drug out once it gets a it gets some pressure on it. And then instead of having the hole open what they have done is, they have put a flow moderator and what this does is this flow modulator will then kind of modulates the flow.

So, even if, lot of pressure is there it kinds of allows you to not let all that drug come out immediately and prevents leaks and all. So, the concept is of-course, the rate of delivery is controlled by the water permeability. So, as the water is going to permeate into this membrane, into this osmotic layer, it is going push on this impermeable reservoir and that is going to essentially drive your drug out.

This is independent of the drug formulation so, in this case like unlike in the previous cases that I was saying that you can not use high molecular weight drugs, only low molecular weight drugs are possible because of the diffusion through this polymer membrane. This one does not even have a polymer membrane it is a whole you can define the size of the hole it could be 1 nanometer, it could be 10 nanometer, it could be hundred nanometer. So, any bigger objects can also come out there is really no limitation to that.

So, typically the rates that this company is able to achieve is between 0.11 to 10 micro liter per hour and then of course, that gives you quite a bit of range to play around with. They have been used for anything between 1 day to 6 weeks for a constant release, again it is going be a 0 order release since the reservoir system.

And as I said flow modulator is to prevent any kind of diffusion so, it is said little bit of back pressure that is there. So, only if there is a good enough pressure coming in from the osmotic layer only then the drug can actually come out and as I also mentioned if even if let us say there is some accidental problem with the pores or with the device, it acts as some kind of a prevention of large accidental spill from happening.

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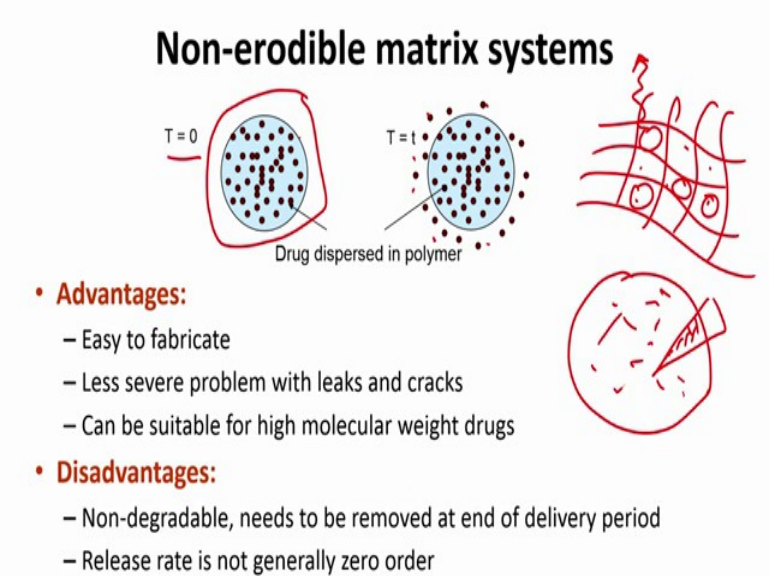

So, next thing we are going to talk about is non erodible systems. So far we were talking about reservoir systems and now we are going to talk about non erodible systems. So, what is non erodible systems? These are systems like this, you have any kind of device which is filled in with lots and lots of drug there is no reservoir here, the drug is well distributed into the device in a in a matrix.

So, this could be a polymeric matrix, if I zoom in to this, these could be polymer chains and then the drug is entrapped in the gaps in these polymeric chains and well separated from each other. But they would still need to somewhat maneuver their way out through the pores of the polymer matrix to come out and that is how they will come out the polymer matrix is not going to undergo any change at least biologically.

And so, that is how at time T equal to 0, it would look like in a time T and there is some drug that has started to come out, but there is still lot of drug is demeaning inside this non erodible matrix. So, that advantage is very easy to fabricate all you have to do is just mix a polymer with the drug at time of polymerization and then whatever shape the polymerization is you will essentially get that. There is really no problem with the leaks and cracks. So, let us say if I have this polymeric device containing lots and lots of drug, even if it gets cracked in one location, only a little bit of the drug is going to come out rest of the drug is still preserved in the polymer matrix.

So, these are not an issue, it can be suitable for high molecular weight drugs. So, it just depends on what is the pore size of these polymer membranes or the polymers that you are using. So, you can use all kinds of drugs in this example; however, some of the disadvantages are this is again non degradable. So, first you have to do a surgery to put it in and then you do a surgery to remove it and the release rate you will get is generally not 0 order, it will depend on what is the concentration remaining in this particular matrix.

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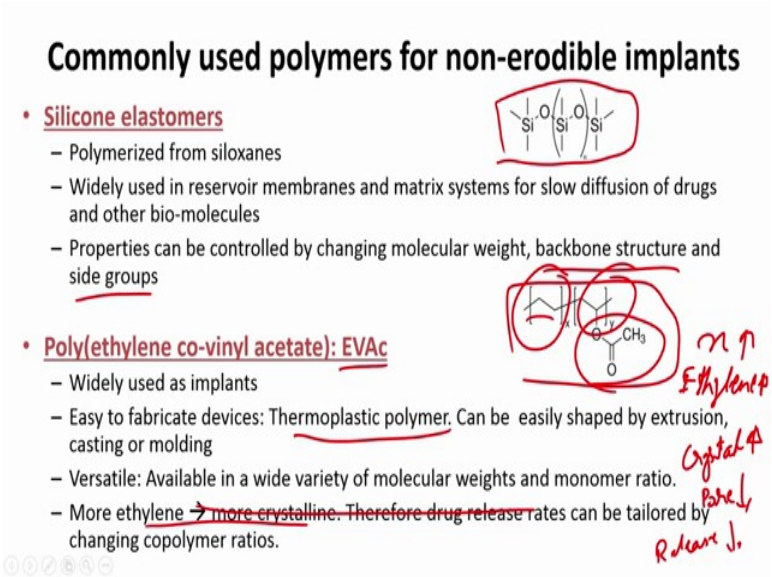

So, some of the commonly used polymers for such kind of non erodible implants, silicone elastomers are used quite a bit. So, these are polymerized from siloxanes, very widely used, both in the device systems as well in metric systems for slow diffusion of drugs and other molecules. Their properties can be controlled by changing the molecular weight.

So, you can change the molecular weight of these polymer chains that you are using, you can change the backbone structure to make it more hydrophilic or hydrophobic, and using the side groups and all of that will essentially change the properties of the polymer. The tc the tm as we discussed previously and depending on that the pore size will change and that drug delivery rate will also change.

Another one that is very widely used is poly ethylene co vinyl acetate, also known as EVAc, again widely used for implants easy to fabricate it is a thermoplastic polymer. So,

you can easily shape it into whatever you want, you can cast it, you can mold it. Very versatile and available in a wide variety of molecular weights, so that allows you to control what is the pore size and what you can then tune on the base of the drug size to essentially get a system that is kind of compatible with all kinds of drugs.

And here is just the structure here, so it is essentially polyethylene. So, this is polyethylene and this is the vinyl acetate group being attached as a copolymer. And remember if you have more ethylene it will make it more crystalline and therefore, the drug release rates can also be altered by changing the ratio of this x and y. So, you can have more x and that will essentially the x increases or in this case x is ethylene.

So, if ethylene increases, then it is going to be more crystalline; that means, crystallinity increases; that means, the pore size will come down and if the pore size is coming down then release rate is lower. So, just one example of how you can change the release rate as required for your application.

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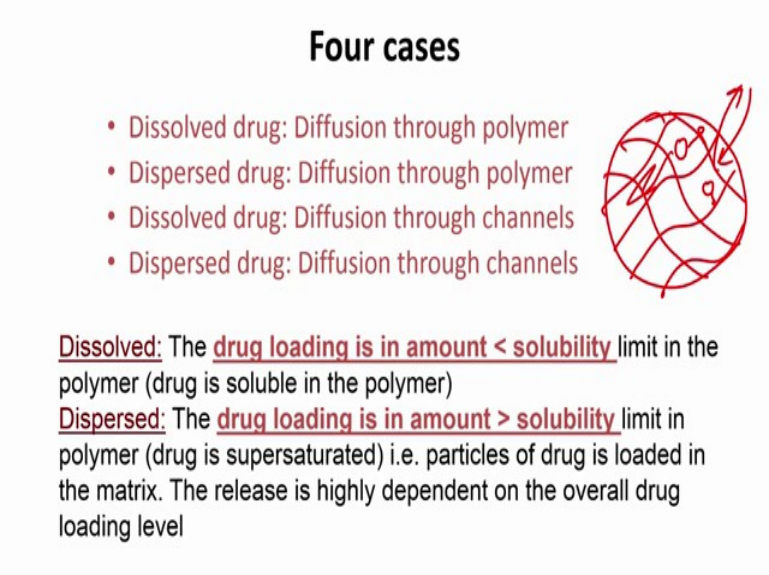

So, to model this again there are four cases that can happen in non erodible systems, one is that the drug is actually dissolved and diffuses through the polymer. So, other case is the drug is not actually dissolved it is precipitated, but it is dispersed in the polymeric system itself. The drug can be dissolved and can freely move around all the drug can be sort of dispersed and precipitated somewhere and it needs some solvent to come in

dissolve it and then take it out or it could be dissolved, but then the polymeric pores are very tiny for the drug to diffuse through.

So, it needs some small channels through which the drug can actually come out and the from the drug of the matrix it would not be able to move through and in the same case, but with the drug precipitates. So, the first the water has to go in those channels and then take the drug out from those channels and we are going to talk about these in more details today. So, as I said dissolved is basically the drug loading is in amount which is less than the solubility limit and the polymer.

So, if that is the case then you have the drug amount which is lower than their solubility limit, so; that means, that drug will remain as soluble and dispersed is the vice-versa. So, if you have if you load the drug in more amount then the solubility in that particular polymer, then those drugs will precipitate and essentially at that point the drug is supersaturated and it is dependent on some other solvent to come in and take it out.

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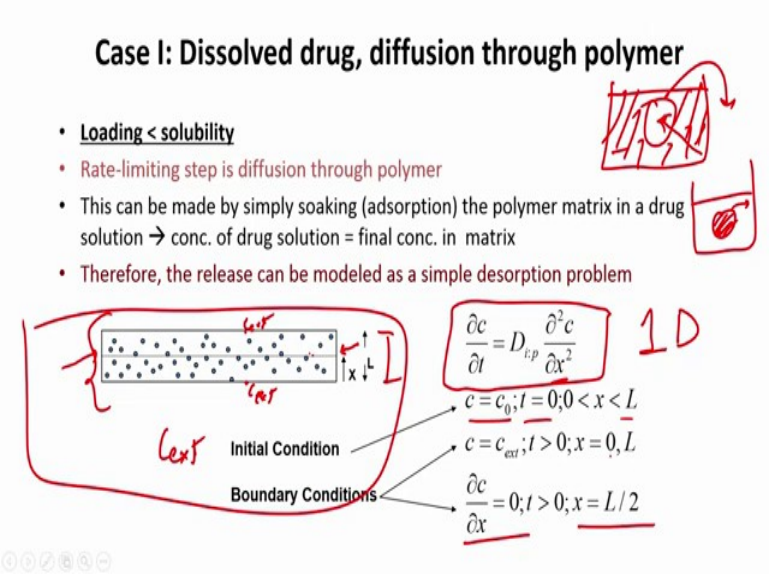

So, let us take it case by case. So, the case I is the drug is dissolved and then it diffuses through the polymer, so basically saying that, the loaded amount of drug is less than the solubility of the drug in that particular polymer. So, then the rate limiting step is just the diffusion through the polymer, so the drug will just diffuse around and then soon as it finds the pores in the polymer to come out, it will just come out.

So, to make this device you do not even have to load the drug first you can make a device since this device is big enough pores for the drug to go in and come out and the drug is soluble in the device. So, you can just make the device soak it in a super high saturated concentration of the drug and then the drug will essentially just diffuse in and then you take this device out and implant it in something that does not contain drug and then the drug will come out.

So, essentially this kind of using the osmotic gradient of the drug itself to kind of load and release. And if you leave it long enough, then the concentration, you know the concentration of the drug since it is soluble it will go in and it will be the whatever was the concentration in the solution will be the concentration in the final matrix. So, in this case, you can just model the release rate using a simple desorption problem.

And so, just an example here so, let us say your device has a total thickness of L and we want to define it as a function of X. So, right at the center will be least amount of drug coming out; obviously, and this will be the last drug that will come out, the one at the edges will come out immediately. So, again going back to Fick's law, in this case and we are only talking about one dimension. So, we are talking about 1D.

So, it is only x that is present the y and z are not there and so, if you want to define some initial condition, you can define it on the basis saying that

$$c = c_0; t = 0; 0 < x < L$$
$$c = c_{ext}; t > 0; x = 0, L$$

So, basically saying at the boundary since this we are considering a large media through which drug is going to be uniformly distributed, let us say this is c exterior. So, at the boundary it also has to be c exterior for continuity right.

$$\frac{\partial c}{\partial x} = 0; t > 0; x = L/2$$

So, right in the middle there will be no change because it is going to be similar on both sides.

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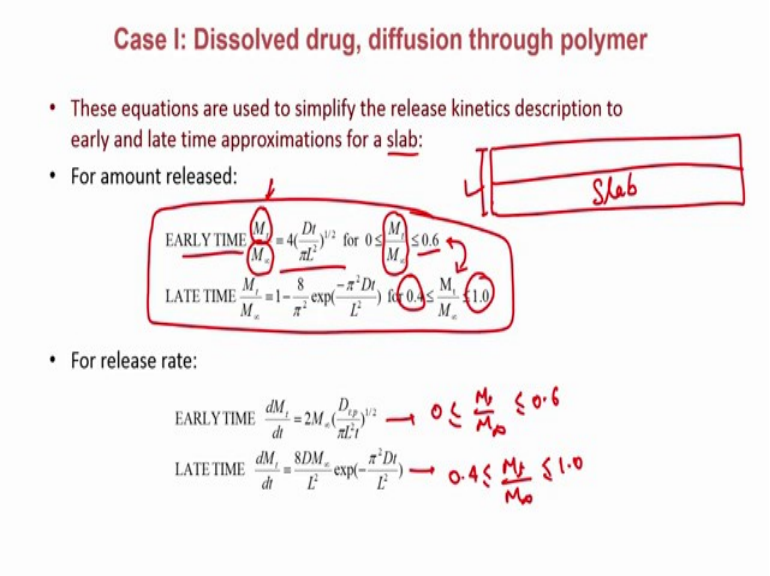

So, we can solve these equations further and we can get the release kinetics at different time points. So, what is done in this case is, if you solve these it will result in a very large equation with lots and lots of terms, but you can then do some approximations for early and the late time points. So, this is; obviously, we are talking about a slab which is long. So, here is your slab from the previous slide which we are saying is a length of L.

So, for the amount that is released at any time t the solution it will boil down to basically these two equations. This is for the early time, where Mt represents the amount of drug that is being released at any time t and Minfinity is the total amount basically the amount of drug that is released at the time infinity and if you do an approximation saying that if Mt by M infinity.

So, only about 60 percent of the drug or less is released you can use this equation which is in a very simplified format it is nothing, but,

$$\text{EARLY TIME } \frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\pi L^2}\right)^{1/2} \text{ for } 0 \le \frac{M_t}{M_\infty} \le 0.6$$

where L is the thickness of this slab. And for the late time point you can then neglect some other terms from that large equation and you will get an equation which is again is in that approximation. So, for anything between 40 percent to 100 percent you can do this approximation, so as you can see there was a bit of overlap here.

So, between 0.4 point 0.6, you can use any of the two equations and they will give very similar values, and then you can; obviously, differentiate it so, this is the total drug that is released, but if you differentiate this equation with respect to time you will get what is the release rate at that particular time so dM by dt and that will be then represented this is nothing, but differentials for these. And again this will be presented this will be from 0 to 0.6 so, for 0 to 60 percent of the drug being released and this equation will be for 0.4 to 1.

So, 40 percent 100 percent and these are the terms that you will get again you do not need to remember this if we do have any questions we will give you the equations you just need to know what these terms mean and how is the significance in terms of drug release.

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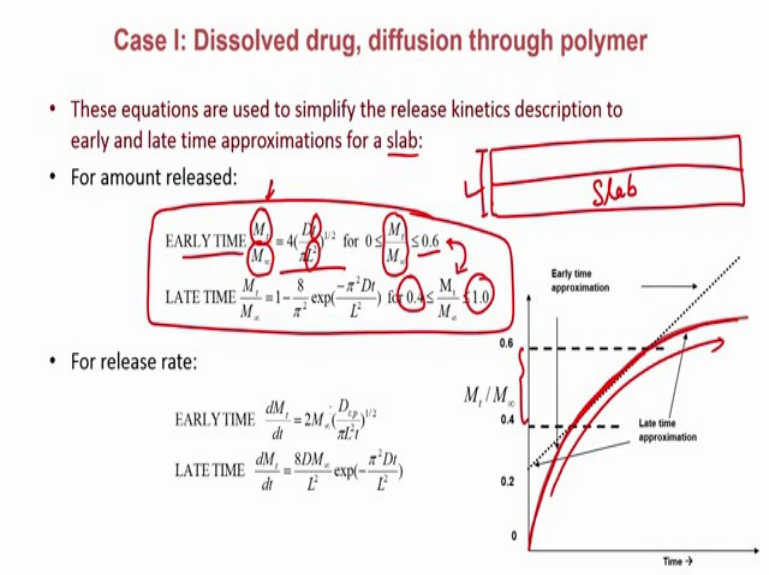

And if I then graphically plot it, what you end up is with a graph like this and as you can see from the 0.4 to 0.6 both of these will be valid and so, this is the late time approximation, this is the early time approximation and that is how you will see the release rate over time. So, it will start to be higher just because there is quite a lot of drug, but as the amount of the drug decreases, the release rate will continue to decrease.

So, if I have the slab and now if I have to change the release date, I can easily change it by either changing this length, the L or by changing the time, it will all change according to that.

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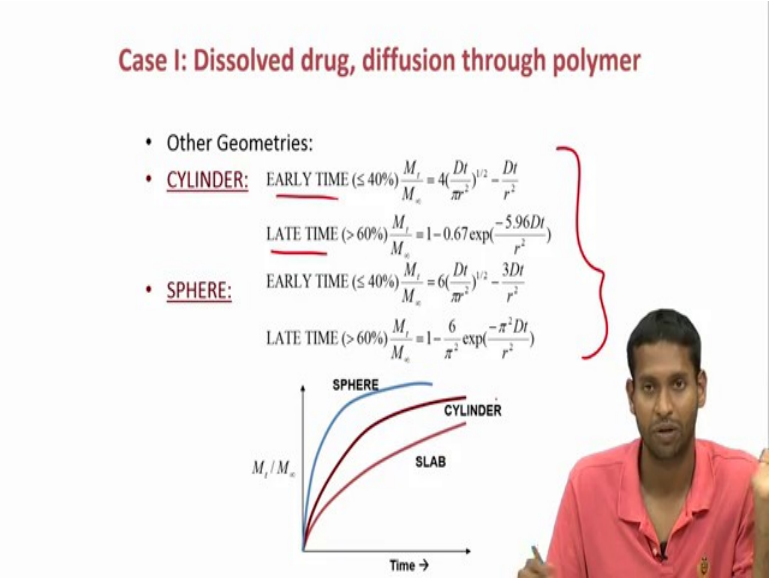

So, if you then solve this for different geometries you get different results again it becomes a large equation that if you use long enough time, you can neglect some terms and if you use early times, it is defined by some other mechanism. So, these are how the equations come out to be you do not really need to remember these, but this is just for information and what do you find is that the sphere releases very quickly compared to cylinder and compared to a very long slab.

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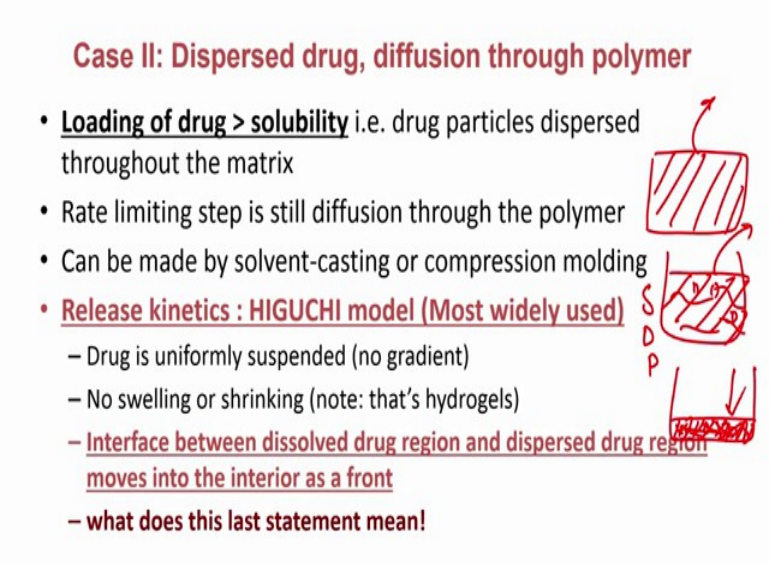

So, this is how just the kinetics is. Now, let us take the second case in which now the drag is not actually not solvable, but it is dispersed. So, the loading is greater than the solubility in that particular polymer. So, again then now the rate limiting step is still the diffusion through the polymer and the drug is still has to come out. This can be made by solvent casting or compression modeling. So, you can have; you can have a polymer matrix dissolved in some sort of solvent and then you evaporate the solvent, the drug was soluble in the solvent, but not soluble in the polymer which is entrapping the drug now once the solvent has evaporated.

So, just to further clarify this, so let us say if I have a solvent. Let us say the solvent is S, which has a solubility of the drug D and the polymer P. Now, there are polymeric chains moving around as well as the drug D is also moving around, but once this the solvent is evaporating what will happen is, this polymer is going to aggregate and make this scaffold and because the drug is cannot evaporate the drug gets entrapped in this even though the drug is not soluble. So, in this case you get a dispersed drug.

So, the release kinetics is usually modeled using a HIGUCHI model, drug is considered to be uniformly suspended and there is no gradient assuming that, there was no sort of gravy and establish at the time of the formation. We assume that there is no swelling and shrinking and this will become important when we talk about hydrogels and we will come to that in subsequent classes.

And what we say then that, when the solvent diffuses in and there is a gradient between dissolved drug and the dispersed drug in the device and so, now, this last statement is very tricky. So, I will explain that a bit in the next one.

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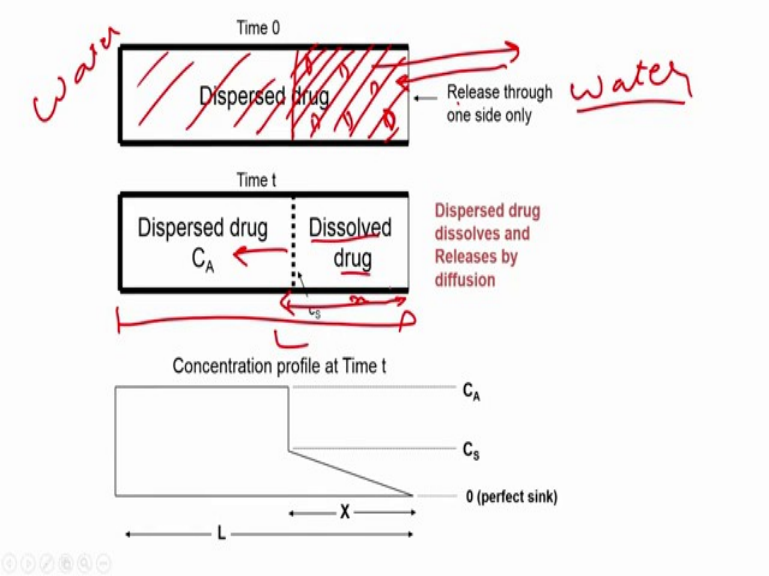

So, let us say this is the device, only one direction it can release. So, let us say there is water everywhere in this device. So, what will happen now when you put this device in this water, the water will try to diffuse in. Now, as the water is diffusing in it could be any of the solvent, but water is more physiologically relevant for most of the things we are talking about in this drug delivery course. So, as water will diffuse in there are throughout this is the polymer matrix and there is drug D that is kind of just suspended and entrapped in here.

So, as the water moves in it will start dissolving this drug D to it is solubility. So, what will happen is, there will be a front in which there will be dissolved drug and then where the water is not present, there will be disposed drug and also not only that why this front will move is because maybe this solubility of the drug in the water is also limited.

So, only when the drug is coming out and this in the concentration in this local environment is below the solubility of the drug in the water. only then it is soluble. So, that is why you will see a front of the drug dissolved drug drag is going to move from the exterior to the interior. And so, the concentration profile of the drug is something like whatever was initially present in the dispersed drug will remain present in the dispersed area.

And so, it would not change at any time t and then at the front where the drug is dissolved it is going a then have on some solubility Cs and then finally, outside we will

say it is a perfect sink which is our tissues, hence it will be 0. So, let us say the length is L and then this is currently defined as the distance x from the exterior.

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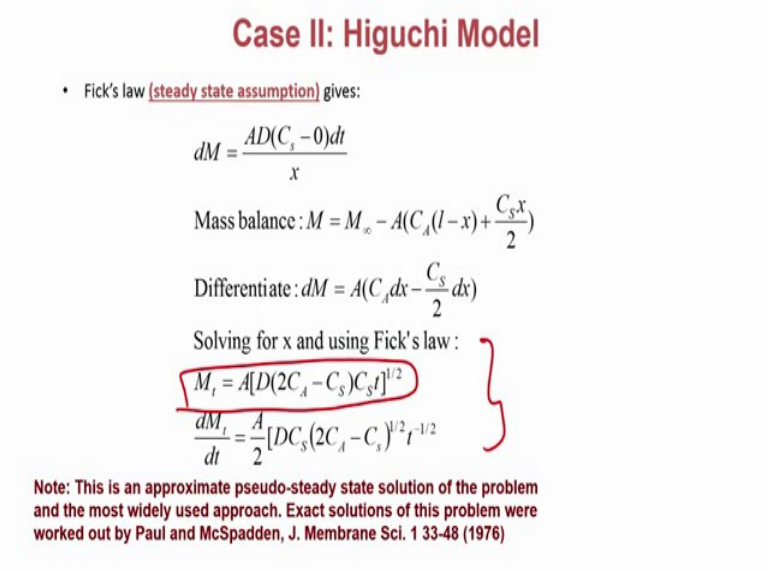

So, now what you can do is you can use some of these Fick's laws and Higuchi model to derive this equation and what you get is essentially this. So, this is how you will model this and this is this is what the final equation at any time be the amount of drug released will look like. Again I will not go into the derivation of this, but you can refer to some of the references I gave at the start of this course, if you are interested in how this drug is diffusing out. So, we will stop right here and we will continue in the next class as to some of the other two cases of the non erodible systems.

Thank you.