Drug Delivery Principles and Engineering
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Lecture – 12
Controlled Release Non erodible Systems and Erodible systems

Hello everyone, welcome to another lecture for Drug Delivery Engineering and Principles. We are now quite deep in the novel systems to kind of do sustained and drug release over a long period of time. And we have done quite a lot of things in the past few classes including polymer drug conjugates then, after that we talked about some reservoir systems. And in the last class we were talking about some non erodible systems. So, let us do a quick recap of what we did in the last class.

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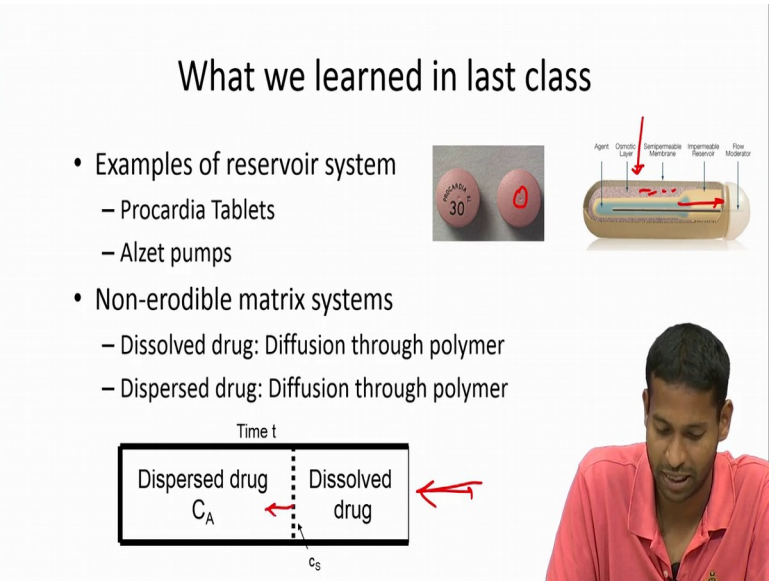

So, in this we first gave you some more examples of the reservoir system one was Procardia tablets. Essentially, tablets carrying a hole in them and osmotically driven. So, the water goes in through the semi permeable membrane and then, pushes the drug to come out; gives you about 24 hours for the drugs to come out before it gets excreted out.

And then, the next thing we talked about was Alzet pumps, very widely used in research for animals and again very similar system, but different design to this. And through which, again the concept is same. The water is going in through the osmosis because of the higher salt gradient here and then, this is pushing the drug to come out through this

pore. Then, we talked about non erodible matrix systems; these are systems which does not erode, but the drug is suspended in them or dissolved in them. Instead of relying in and the water coming in and pushing and driving this force of the drug to come out is essentially this diffusion of the drug through this matrix.

And so, in this one we have four examples or four different cases; out of which we discussed two last time, one was that the drug is dissolved and distributed throughout the polymer and the drug can actually diffuse through the polymeric chains everywhere through the polymer. And then, the next thing we discussed was the same example where, the drug can actually diffuse throughout the polymeric system, but it is not soluble, it is currently dispersed. So, it needs the solvent to come in dissolve it, before it starts its diffusion.

So, the example was given and the derivations were done. And it looks something like this where, you have polymeric system and then, drug is dispersed. And as the water comes in, it dissolves the drug; the drug moves out becomes further soluble and there is this front between dispersed and dissolved drug, that moves towards the interior of the device.

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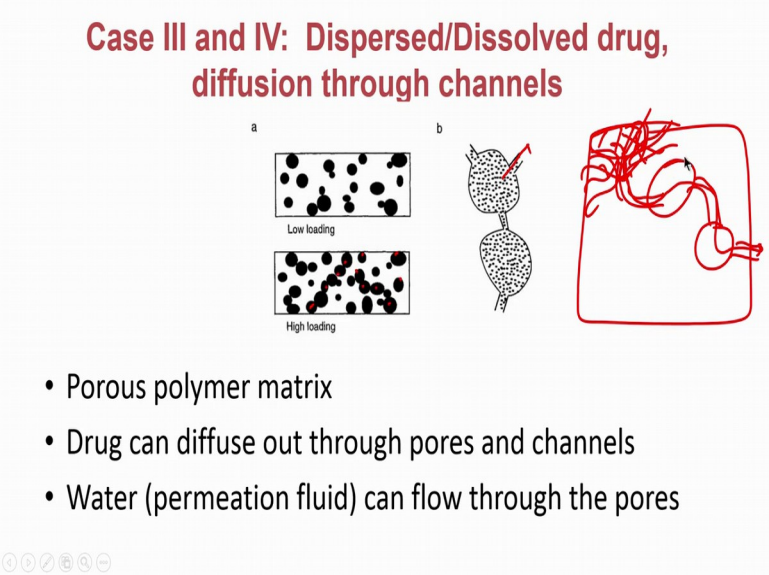

So, let us look at the other two cases of the non erodible system. So, case III and case IV are very similar to what we have already discussed before. So, these could be both dispersed and dissolved in the case III and case IV respectively and it diffuses through

channels. So, what we are saying now is if the device is there at the time of formation there is always some defects that are there.

So, maybe the polymeric chains are fairly close enough, but then, there are always areas where, the amount of polymeric chain might be lower. So, it forms these micro regions, where the drug gets accumulated in the device and it is also connected to other micro regions through small pores, which are big enough to allow that drug to go out.

So, essentially if the drug has to go out from here and all of this is well packed and the drug will have to diffuse from one channel into another reservoir and then, come out from the edge which allows it to come out. And again if the drug is not soluble then, the water will have to go in and dissolve the drug and then, will have to come out through these pores and channels.

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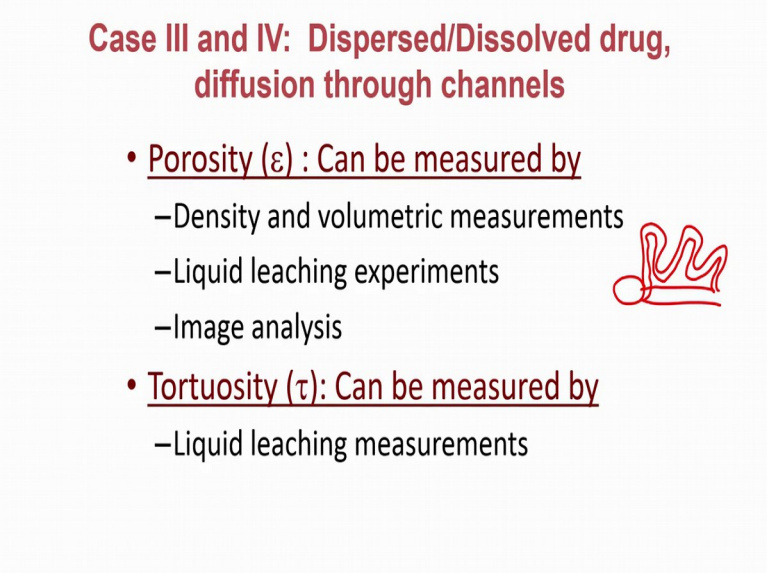

So, how would you then model this? Well, before we do that, we need to define some of the terms that defines these channels and these pores. So, one is porosity, which is defined as what is density of the material is, what volumetric measurements you can do. So, you can do some liquid leaching experiments, you can do imaging, you can look at where are the pores and where the channels and get my idea of the porosity of your device.

And then, the next thing you need to measure is charge tortuosity. So, porosity is essentially just saying that there is pore and how much pores are present in a volume and then, tortuosity is essentially, whether these pores are for a distance are going like this or they are fairly tortuous. And essentially, the drug will have a lot longer path to travel to finally, reach its destination.

So, these two terms; these two we need, would need to define for that polymeric system, for that non erodible system before we can then use it to do the calculations as to what it will be is the release rate.

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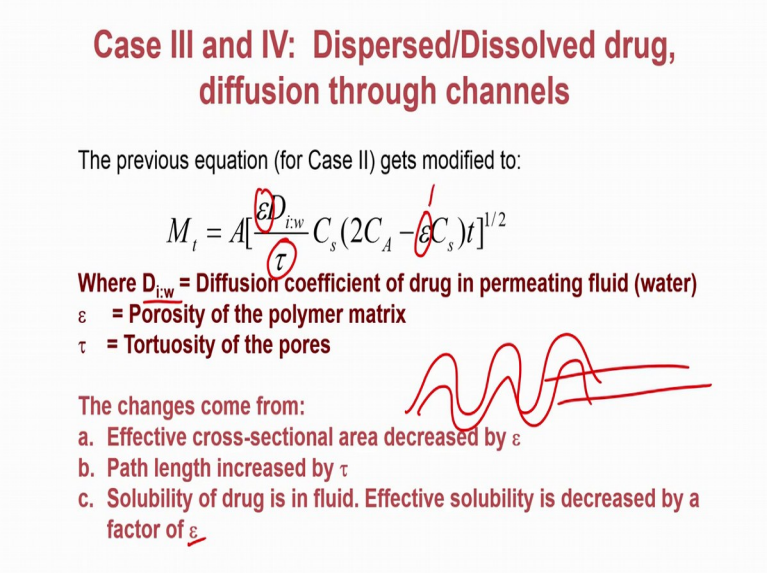

So, it is again very easy. You can take the equation 2 and all you have to do is just supplement it with, instead of the entire volume, you are putting in the tortuosity and the porosity terms.

And of course, the diffusion coefficient will also change because this is essentially a diffusion coefficient of drug in permeating water. So, the water is actually going in and taking it out. So, it has to be the diffusion coefficient in water not the polymeric membrane itself.

So, again as I said the changes come from now that the effective cross sectional area is decreased because of the porosity the path length has increased because of tortuosity as I just said it could; if this is straight, then tortuosity is almost 0, but if this is more like this

then, the tortuosity is fairly high. And then, of course, one of the change is the solubility of drug is in fluid. So, the effect of solubility is decreased by the factor of the porosity; so, now, not everywhere. So, we are not saying solubility everywhere, but by a factor of the porosity.

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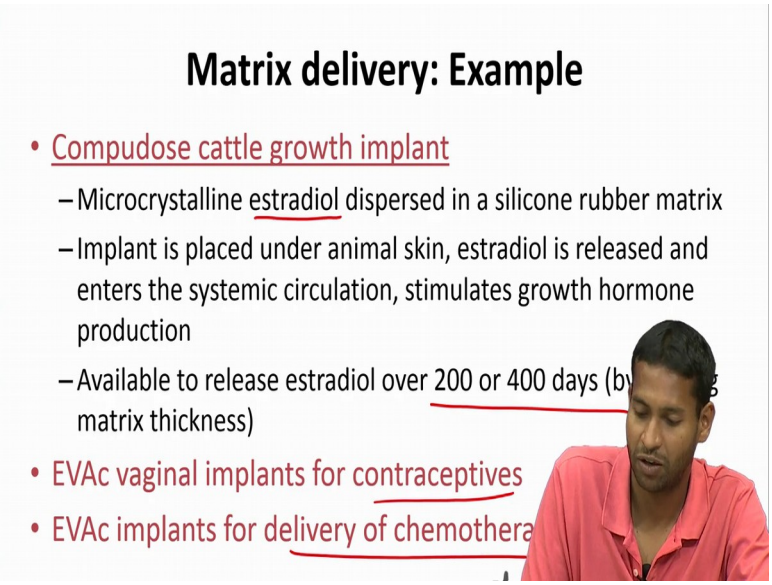

So, some examples of this; one thing that is widely used is a compudose cattle growth implant. So, this is only mainly used for cattle and what is this? This is an implant which releases some growth hormones and some microcrystalline estradiol, which is essentially a growth hormone. And this is dispersed silicone rubber matrix and is placed again under skin of the animal.

And this is then released and go into the systemic circulation to produce growth hormone. Typically, about the release rate can be varied between 200 to 400 days just by varying the matrix thickness. The EVAc vaginal implants are also used mostly for animals again and these are again contraceptive implants. In this case, they are non degradable and the drug has to just diffuse out through them. And then, there is also a EVAc implant that are used for chemotherapy of the brain.

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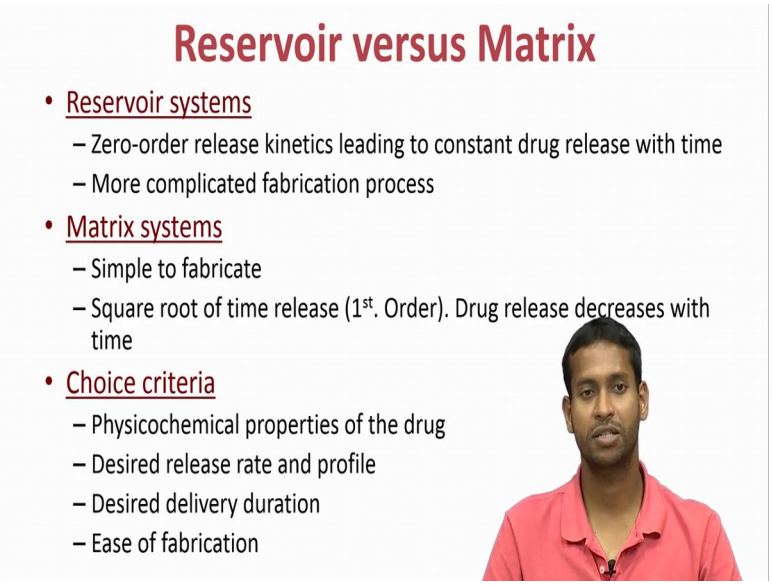

And I will give you more example on that later. So, let us just compare how does the reservoir system stack up against the matrix system. So, in a reservoir system you can get zero order release kinetics. You can get a very constant release rate over time, but the fabrication methods are more complicated compared to let us say a matrix system. In matrix system again, as I said the, fabrication methods are fairly easy, all you have to do is mix things together and kind of polymerize; however, the release rates are typically not zero order. The drug released also decreases over time, is mostly first order or high order kinetics. And so, it is very difficult to monitor what amount of drug may have released in a system, if a clinician will have to look at that.

So, the choice criteria are just depends on, what is the drug? What is the physical and chemical properties? Whether you can get the drug to be soluble enough in high amounts? If the drug cannot be loaded into the polymeric systems in high amounts; then, you will have to go with the reservoir system. What is that desired release rate and profile? Whether he want drug to come out fast in initial times and slow in the later time. Then, you probably want to go with matrix system, which you want it to be constantly release at a constant rate. You want it to be a reservoir system.

How much duration are we looking at? as I just said reservoir systems can be adjusted to have them release over a period of months. Even matrix systems can be done with that, but again it depends on what profile you want and then of course, what facilities you

have in terms of fabricating it, that will also kind of limit you to what you can do and what you cannot.

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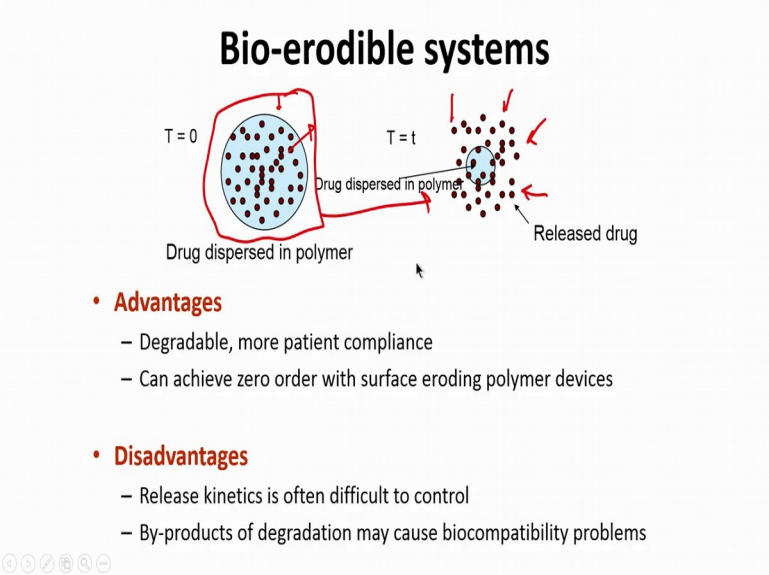

So, the next step we are going to talk about is bio erodible. So, like non erodible systems, these are again matrix type systems, very similar in terms of the initial synthesis and drug loading, but the release mechanism is very different. So, in this case, what is done is typically the drug like the non erodible system is loaded into a polymeric matrix; however, this drug cannot diffuse out the polymeric chains are very tight and the pore size is much lower than the size of the drug. And so the release will essentially depend on the degradation of the polymeric region.

So, as, as time passes, more and more polymer degrades when, it degrades it just releases whatever drug was encapsulated in that degraded area. So, some advantages are: its degradable; so, it is very patient compliance. So, this time you only have to do one surgery because you do not have to ever take it out. After a certain period of time this is going to disappear. you can achieve zero order kinetics this is with an asterisk, not as well as you can do with the reservoir system. But if you have a large enough device and it is slowly degrading then, at least for quite a bit period of time, you can get a zero order kinetics with surface eroding polymers.

But again, this comes with some asterisk over it. Some of the disadvantages are apart from the surface eroding polymer, the release kinetics can be very difficult to control.

And now, not only that, you have to worry about what happens when, this polymer degrades whether the components its degrading into whether they are toxic or not, whether they are causing any adverse effect or whether they are interfering with the drug. So, all of these biocompatibility problem starts to chip in.

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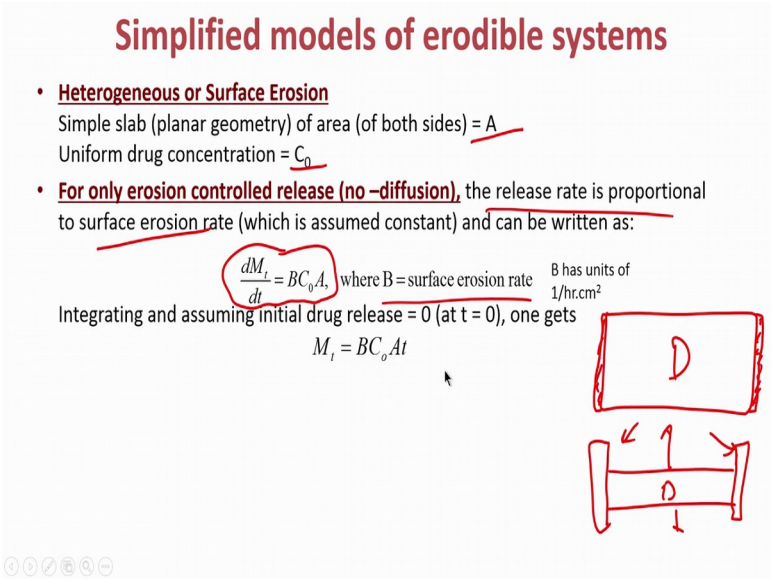

So, some simplified models of erodible systems. So, for a simple slab or planar geometry; let us say that area from where, this is eroding is A and let us say it is uniformly drug concentration of C0. So, if it is only erosion control let us say, there is no diffusion which is how we started defining this that the pore size is much lower than the size of the drug. So, the drug cannot diffuse out. It has to basically, wait for the polymer to erode. So, then the release rate is essentially proportional to what is the erosion rate.

So, the dM by dt is nothing, but the surface erosion rate, which is defined here as B. What is the concentration drug and the area through which it is eroding.

$$\frac{dM_t}{dt} = BC_0A, \quad \text{where B} = \text{surface erosion rate}$$

Remember, this area is of course, going to change over time. So, if I have a device initially which was this and if surface erodes into a device, which is this, the area from which the drug is coming out has obviously changed.

However, for initial time point, this is too slow; then, we can consider it to be similar areas and it could be zero order. The other case could be that, instead of going like this. Let us say, this is non eroding all the edges and only from the two edges it is eroding or the drug is coming out.

Then, in that case you will have this converting to somewhat of a design like this. In which, the drug D is present here. In this case, your area remains constant, but this is very sparingly used now because you leave to non eroding surface is there, but anyway. So, dM by dt can be modeled with the surface erosion rate as described here. So, if you just integrate that you simply get

$$M_t = BC_o At$$

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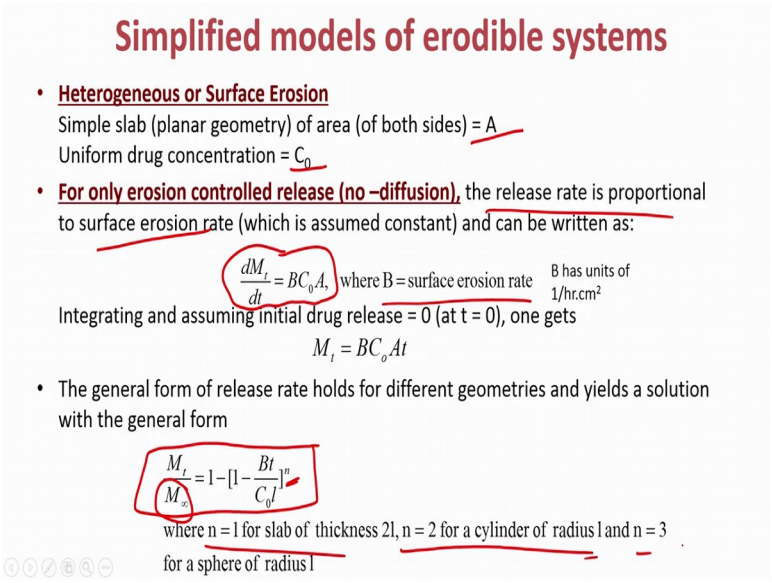

This general form release rate holds for different geometries and if you have to basically make it further generalized, for all kinds of geometries; you can do that. And if you do that what you will find is this general form turns into an equation like this, where Mt is the concentration of the drug released at any time t, Minfinity is the total drug that was loaded and that is a function of the erosion rate as well as time with some n. And this n is what changes for different geometries. So, it is 1 for slab to give you back that equation, it is 2 for cylinder of radius 1 and n is equal to 3 for the radius with the sphere of l.

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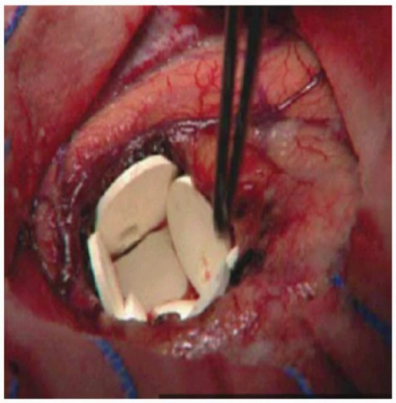

Fig. 4. Gliadel® wafer implantation at tumor resection site. Around 7–8 wafers are placed for localized delivery of BCNU via P(CPP:SA) polymer (Reproduced with permission from [22]).

Copolymer of sebacic acid and carboxy phenoxy propane, and erodes over 6–8 weeks in vivo

So, this is one example and it is a little bit of gory image, but what you are looking at here is a actual patient image of their brain. So, in this particular patient, the brain was surgically removed. the tumor in the brain was surgically removed. The patient contained a big large tumor and the tumor was surgically removed. Now, once the tumor was removed the problem is when the doctors are removing let us say, this is the brain and this is the tumor.

And the doctors are removing this tumor and they have to be careful in what amount of the tissue they are removing; it is very hard for them to know where the tumor ends and where the healthy tissue starts. And since it is a critical organ such as brain, often doctors were being very conservative and they would only take out let us say this area. Leaving a ring of tumor cells or some tumor cells behind, which will then re-grow and cause relapse.

Now, this was a problem because then, the patient will come back in 1 or 2 years and then, most often the tumor will be even more aggressive and the survival rate for the patient was fairly low. So, what they did is that they made these discs shape implants, which were encapsulating anti cancer drugs and what that did is, these were erodible implants and they would release the anti cancer a drug over a period of time. So, about 7 to 8 wafers were placed wherever they wanted to do this. And essentially, over a period

of time, if there are any tumor cells remaining in the surrounding, this anti cancer drug will release out and kill those tumor cells preventing the relapse of the patient.

So, this typically erodes over 6 to 8 weeks. So, by the time 2-3 months are gone there is nothing remaining. So, there is no repeat surgery that the patient has to undergo to remove these and hopefully and none of the tumor cells will re-grow.

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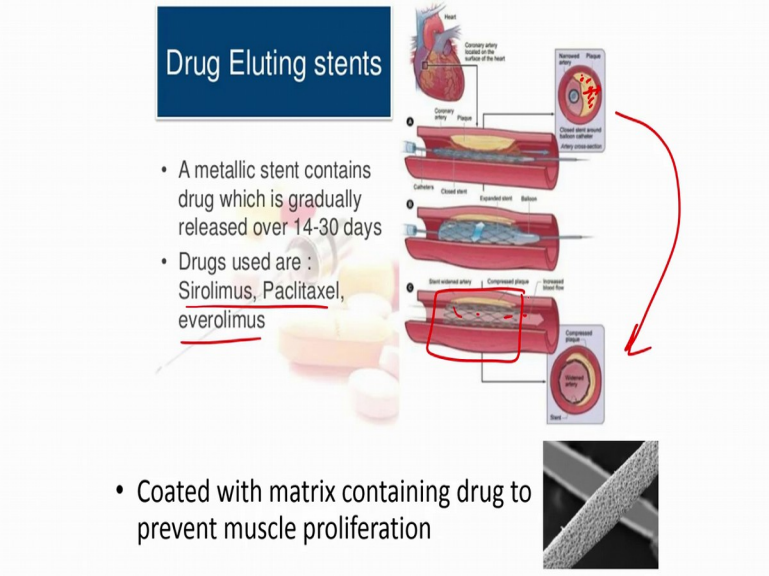

Other examples here are drug eluting stents. These are essentially metallic stents contains drug which is gradually released over a period of 14 to 30days.

And so what it is; is essentially, what happens in, in case of stent is that a stent is put in the body when, there are plaques. And plaques are nothing, but these growth of the vessels. So, the vessels essentially thins because there is sort of some inflammation and there is some sort of a plaque deposition, some bio material deposition onto your vessel which makes it thinner and thinner.

Now, because this is getting thinner and thinner what happens is, downstream these cells that need oxygen and the glucose from the blood and they are not able to get enough oxygen and they start to die and this is essentially a region for heart attacks especially, in the heart region.

And so, what is done is something where, a metal wire is put in with a mesh with a stent, which looks like this and this stent then, used to basically expand the blood vessel. So,

essentially compress the plaque back so, that the blood vessels open up and the downstream cells can get enough oxygen. So, this will turn into this after the whole procedure and the problem is now because you are putting some mechanical stress on the surrounding area, the surrounding area cells are not very happy there are all kinds of inflammation, in all kinds of proliferation it starts to happen.

And to prevent that what is done is an anti inflammatory drug or an anti proliferative drugs is given and the easiest way to given it is just coat these metals with some polymeric membranes that are encapsulating some of these drugs and these drugs will then come out over time and ensure that the cells in the surrounding for this region are not misbehaving. Because otherwise, if that happens then the stent will fail and more plaque will go in this region. So, this is done to prevent that; to prevent muscle proliferation from happening in the surrounding area.

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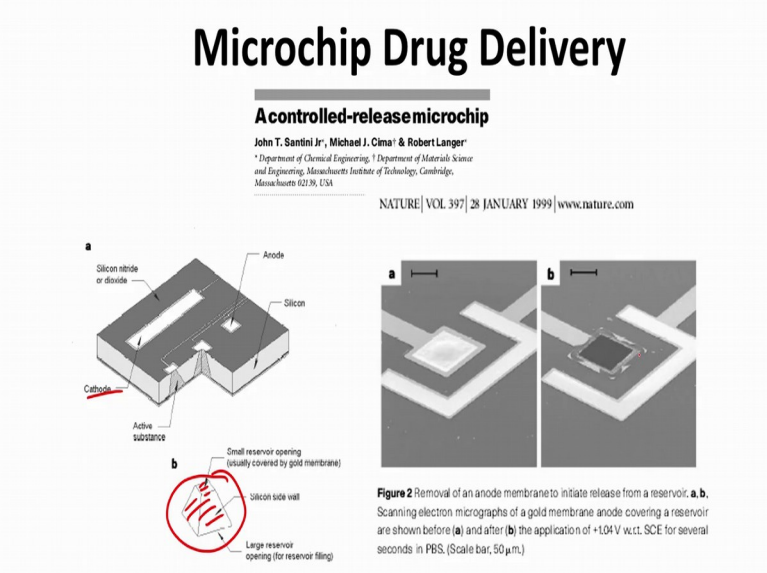

Here is another example, this is microchip delivery. So, what it is? It is essentially some fancier system. So, this is not essentially erodible system or a matrix system. In this case, what the authors have done, this is still in the research phase, but what the authors have done is they have synthesized a reservoir type system here with some very thin cathode which could be made of any metal. So, if you zoom into this; you see a structure like this where, the reservoir of drug is here and this is capped by a thin cathode or thin anode and if you essentially pass current through it. It heats up and gets degraded and once it gets

degraded all the drug which is there is going to come out. So, in this case you want to give a bolus delivery of the drug.

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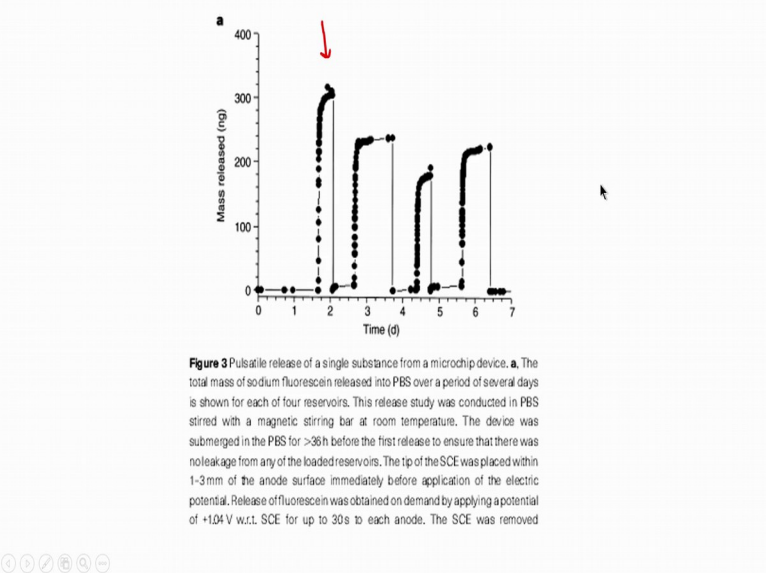

Figure 3 Pulsatile release of a single substance from a microchip device. **a**, The total mass of sodium fluorescein released into PBS over a period of several days is shown for each of four reservoirs. This release study was conducted in PBS stirred with a magnetic stirring bar at room temperature. The device was submerged in the PBS for >36 h before the first release to ensure that there was no leakage from any of the loaded reservoirs. The tip of the SCE was placed within 1–3 mm of the anode surface immediately before application of the electric potential. Release of fluorescein was obtained on demand by applying a potential of +1.04 V w.r.t. SCE for up to 30 s to each anode. The SCE was removed

So, the profiles would look like this. So, you can essentially give current and you will see that suddenly one drug in one of the reservoir has come out.

You can give let us say, this, this and this. So, you can get multiple types of drug coming out at different time point whenever you need them. So, this can be for something like a vaccine shot. Let us say you want vaccine shots once every week. You can use such a system for that still not clinically used, but something that can be of a good use if required.

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Multi-pulse drug delivery from a resorbable polymeric microchip device

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nature materials | VOL 2 | NOVEMBER 2003 | www.nature.com/naturematerials

You can then, actually instead of relying on the current, you can then, put these membranes which degrade over time by themselves, in presence of water and this is what paper describing that.

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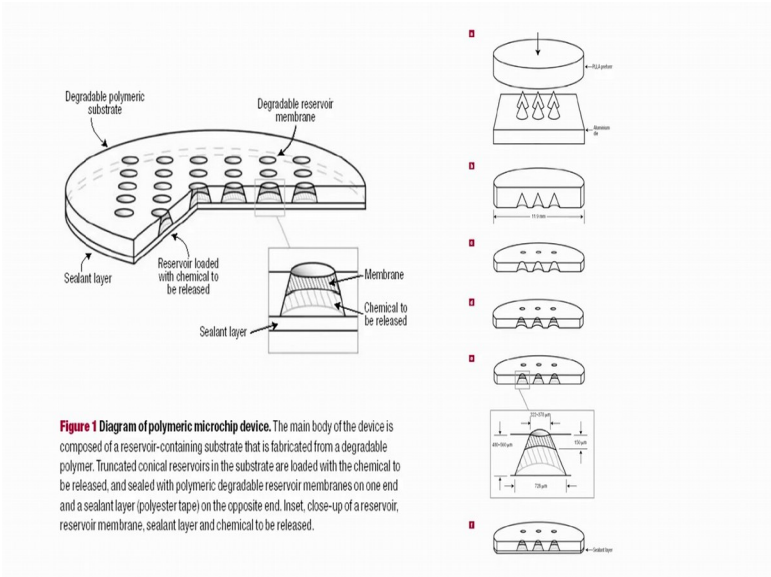

Figure 1 Diagram of polymeric microchip device. The main body of the device is composed of a reservoir-containing substrate that is fabricated from a degradable polymer. Truncated conical reservoirs in the substrate are loaded with the chemical to be released, and sealed with polymeric degradable reservoir membranes on one end and a sealant layer (polyester tape) on the opposite end. Inset, close-up of a reservoir, reservoir membrane, sealant layer and chemical to be released.

So, what they have done is the same thing they have made some reservoirs and then, they have capped these reservoirs. So, how this is how these reservoirs are made through some lithography techniques.

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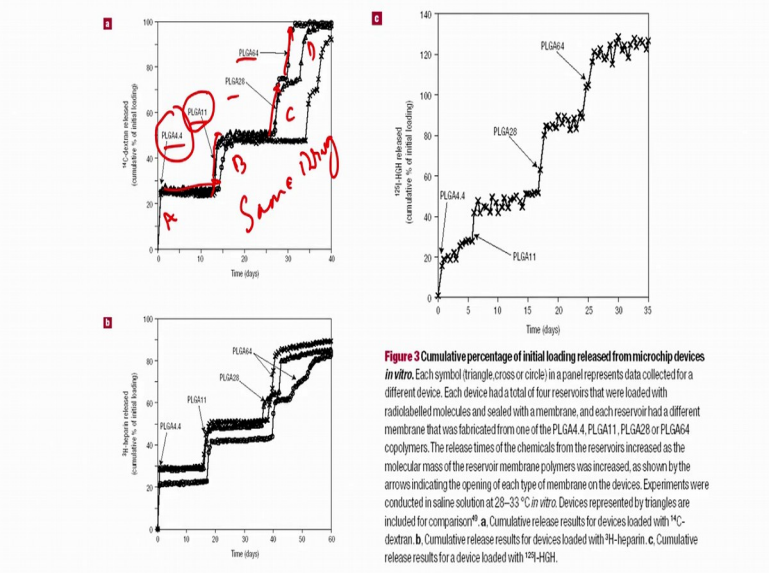

Figure 3 Cumulative percentage of initial loading released from microchip devices *in vitro*. Each symbol (triangle, cross or circle) in a panel represents data collected for a different device. Each device had a total of four reservoirs that were loaded with radiolabelled molecules and sealed with a membrane, and each reservoir had a different membrane that was fabricated from one of the PLGA4.4, PLGA11, PLGA28 or PLGA64 copolymers. The release times of the chemicals from the reservoirs increased as the molecular mass of the reservoir membrane polymers was increased, as shown by the arrows indicating the opening of each type of membrane on the devices. Experiments were conducted in saline solution at 28–33 °C *in vitro*. Devices represented by triangles are included for comparison[8]. **a**, Cumulative release results for devices loaded with ^{14}C-dextran. **b**, Cumulative release results for devices loaded with ^{3}H-heparin. **c**, Cumulative release results for a device loaded with ^{125}I-HGH.

And what they have done is they then capped at with different kinds of polymers in different molecular weights. So, depending on the different molecular weights in this case PLGA, the degradation of that particular polymer is different. So, PLGA with the lower molecular weight; in this case, 4.4 kilo Dalton will degrade faster.

So, that reservoir will open up and release whatever drug was there. If all the reservoir contain the same amount to drugs, similar types of drugs then, the other one 11 kilo dalton will degrade, it will open up that channel and that is how you can have sequential release of the drug.

So, these could be same drug or you can have different drugs coming out too. So, maybe this is drug A, this is drug B, this is drug C and so that is how you can do that, but note that there will be some variability notice that there are different profiles or at different time points these things have degraded. So, that is just something that you will have to control, but you can have such type of systems as well. You do not have to rely for external stimulus, but the membrane itself will degrade ok. We will stop with this today. We will continue this further in the next class.

Thank you.