Drug Delivery Principles and Engineering
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Lecture - 37
Route Specific Delivery Oral and Subcutaneous Route

Hello everyone. Welcome to another lecture for Drug Delivery Engineering and Principles. We have been talking about routes of administration in this module and the first thing we are talking about in the different routes is the oral route. So, let us quickly recap what we learned in the last class.

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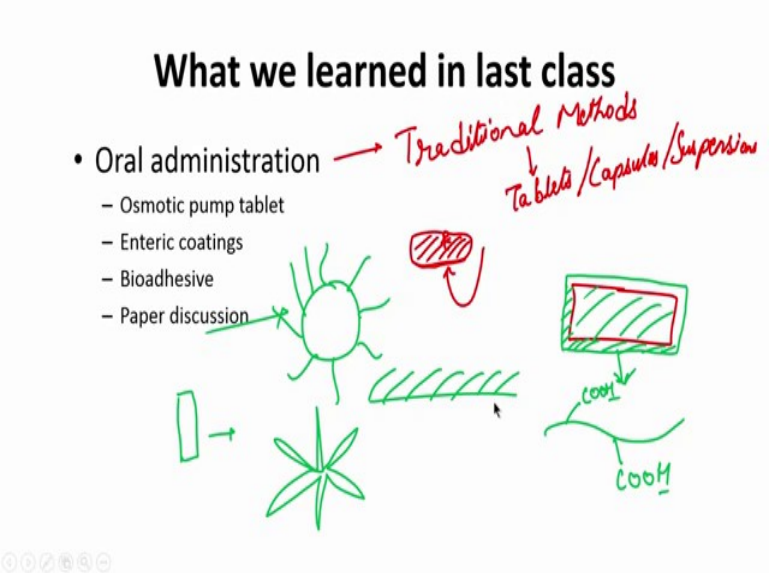

So, one thing as I said we were discussing oral administration. So, previously a class before that we are talked about various traditional methods, and those were tablets, capsules, suspensions. Again, very successful very widely used I am sure all of you would have taken one or the other form multiple times in your life, but they have their own shortcomings as well, lots of them actually, and that is why there is a need for innovations. So, we are now discussing as to what innovations can be done.

So, in the last class we talked about few things. We talked about an osmotic pump tablet which is nothing but a tablet with some hole in it, and this is filled with drug as well as some high concentration of ions, protected by a semipermeable membrane. And it is basically a mini pump, so as the surrounding water tends to move in because of the

osmotic pressure, which we can define by the van't Hoff equation, the pressure inside increases and then it forces the drug to come out from this orifice. And depending on the size of the orifice and the type of the drug you can control the release. So, that gives you quite a bit of maneuverability because you can now have the release happen over a longer duration rather than tablet just getting disintegrated. So, typically we are talking about anywhere between 12 to 24 hours instead of 2 to 5 hours what do you typically get with these tablets.

Then we talked about enteric coatings, enteric coatings are a very nice concept in a way that this can be used on most forms of delivery through oral route. So, you can actually use enteric coatings on tablets as well. And what is done is let say if this is a tablet, then you can just coat it with some polymers with certain characteristics and that is what we are calling is enteric coating. And these polymers are nothing but polymers composed of polycarboxyls and because of that they have some pH responsiveness, where at low pH these will be protonated and will have low solubility, but at higher pH these will become ionic and have very high solubility will dissolve away and only then the drug will get released out. So, that way you can prevent the drug from harsh environment.

And then the last thing we discussed in different strategies was a bioadhesiveness. So, you can make particles containing various long polymers hanging out from the surface and these can then go ahead and interact with the mucin or the mucous layer that is present on your oral route. So, that can then increase the residence time because it will not flow as fast when these polymers start to entangle with each other.

And then finally, we had a paper discussion in which we had talked about some of the more advanced ways, although these are still in research. Where, in this particular paper we are talked about a capsule which looks like a normal capsule, but once it goes in the stomach it opens up into 6 different branches and become so large that it cannot really move out from your stomach cavity. And that increases the residence time in the stomach cavity, and the authors in this particular paper showed that this could be increased all the way up to 10 to 14 days.

So, in this class we will also discuss another paper more on the oral administration route.

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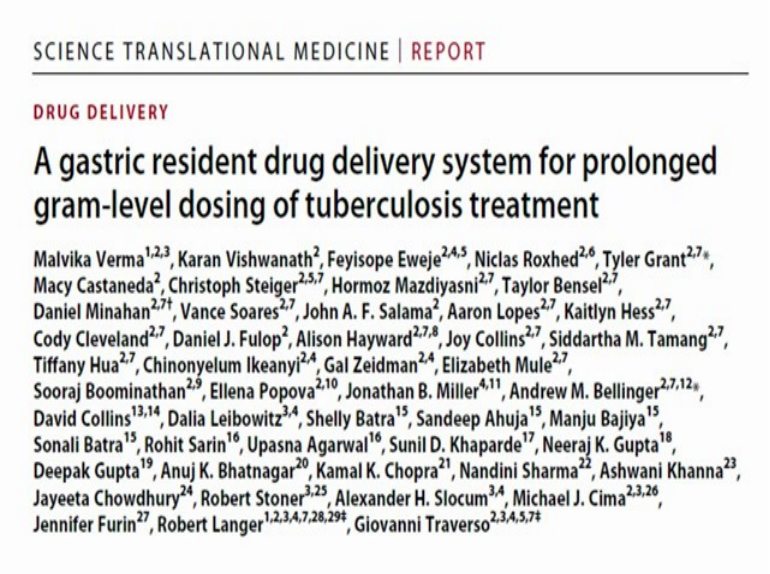

And this is a paper that was published fairly recently.

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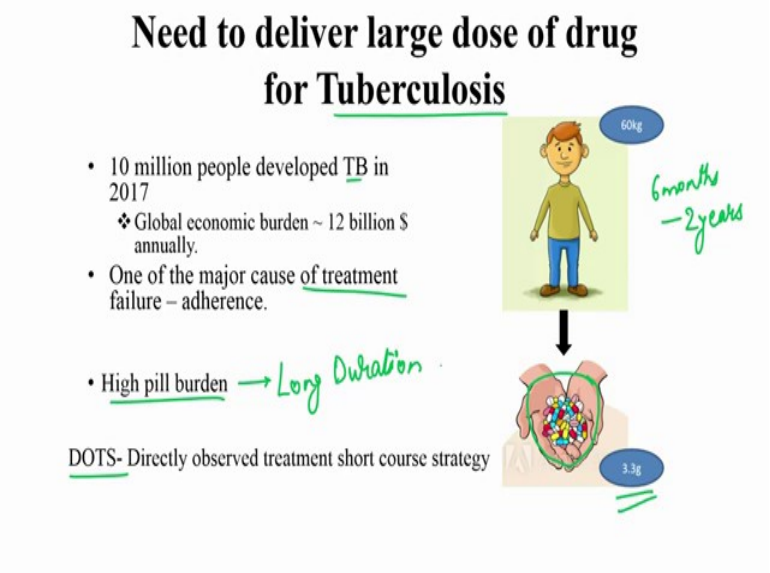

This paper is for the treatment of tuberculosis. So, last paper was on malaria. In this paper we will focus more on tuberculosis. Tuberculosis is a very severe disease, just a little bit of background almost 10 million people developed active TB in 2017 and there is a quite a bit of global economic burden because of this disease. And one of the major problem with this disease is the long duration of treatment.

So, typically a patient would have to take quite a bit of tablets and not only that, they will have to take tablets for a period duration of anywhere between 6 months to 2 years. And that is a strong burden on the patient to remember taking tablet each and every day. As long as the patients are sick they still remember it but once they start improving their health, they feel that they do not need the tablet anymore, they stop taking these tablets that then makes the problem even worse because then the patient bacteria can develop resistance because you are not able to kill it off you have just given it a small stress and the bacteria will evolve itself to be able to overcome that small stress. So, that is a major problem.

The other problem is the amount of tablet that is required. So, as you can see for a 60 kg human you are looking at almost 3.3 gram of tablets that the patient has to take every day, and so that is a big burden on the patient again and decreases the patient compliance. So, there are some of the programs that government have started to tackle this. One program which has been fairly successful is called dots and dots is nothing, but a directly observed treatment short course strategy, where what is done is there are small clinics that established and the patients actually come to the clinic and they are administered these tablets in presence of a government folk that make sure that patients are actually taking the tablet.

In case the patients are not coming they can go to their houses and again make sure that these tablets are delivered. Again, it is fairly successful, but then the problem is that lot of manpower is involved and not to mention then the patient can still decline to take the drug. So, again as I said one of the major causes of the treatment failure is the adherence to the treatment, patients do not adhere to the treatment and a major part of that has to got to do with the high pill burden as well as long duration.

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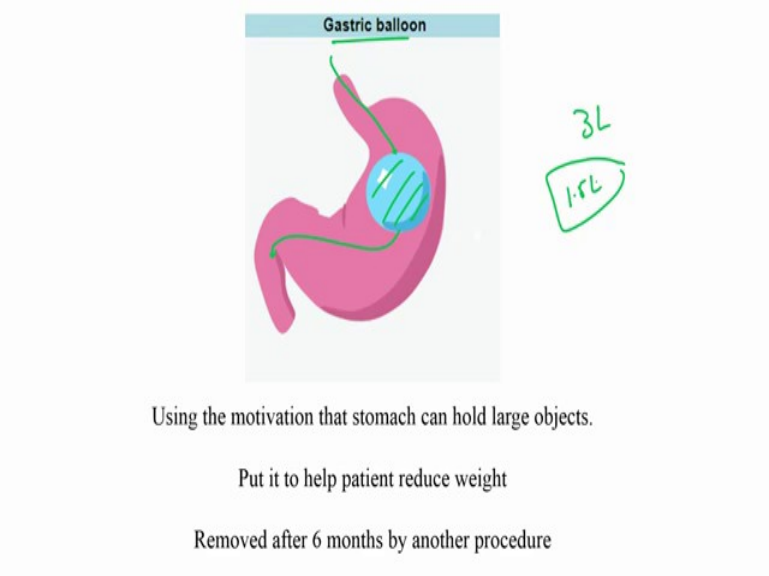

So, what is the alternative? So, now, that we are looking about delivering grams and grams of drug in this particular disease, the motivation then comes from the fact that our stomachs can actually hold very large objects. So, here is an example, here is a gastric balloon and what it is - an inflatable balloon which is put into a patient's body. So, this is put in the body it is then inflated and the size becomes so large that, first of all, it cannot exit through the stomach pylorus cavity and it resides in the stomach and because it is so large what happens is the volume of the stomach decreases.

So, earlier let say if your volume of the stomach was 3 liters, now you have put a 1 liter or a 1 and a half liter in here. So, your effective remaining volume is only 1 and a half liter. So, earlier if you had to eat or drink 3 liters of food, but the food or 3 kg worth of food to feel full, in this case now you will start feeling full only at half of that amount. And so that basically reduces the amount of consumption of food that you are in taking and that helps patient do reduce weight.

So, this is typically done in a very severe obesity cases where the BMI index has gone off the roof and the patient is very susceptible to all kinds of metabolic activities. And this gastric balloon has been found to safe for all the way up to 6 months, where people then start losing weight and then different people have different efficacy for this, but people have seen reduction in the weight from all the way to 5 percent to 30-40 percent. And then after 6 months this balloon is removed because due to repeated use of this

balloon every time you eat things the balloon becomes weak and there is a chance that it might rupture. So, just to be on safe side it is removed after 6 months. What this shows it shows that first of all stomachs can take large objects and then these large objects can be there for up to 6 months or more if they are stable.

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So, that is what the authors have drawn their motivation from. So, some of the advantages for the gastrointestinal tract delivery is first of all ease of administration. So, again they do not really want to do a surgery, they do not really want to go for the injections just because this is a duration of 6 months to 2 years and they do not want the patients to become even less compliant than what they have already are. This route is fairly immunotolerant. So, even though technically speaking its inside the body, the immune system does not really see it as inside the body.

The immune system does not really survey the lumen of the stomach or the intestine as strongly as it does let us say blood or other organs. So, even if you put anything immunogenic, it is more likely that the body is not going to respond to it very strongly. And then because of the size, you can accommodate gram level dosing, you can accommodate as much dose as you want pretty much for a human because you have a lot of space to play around with.

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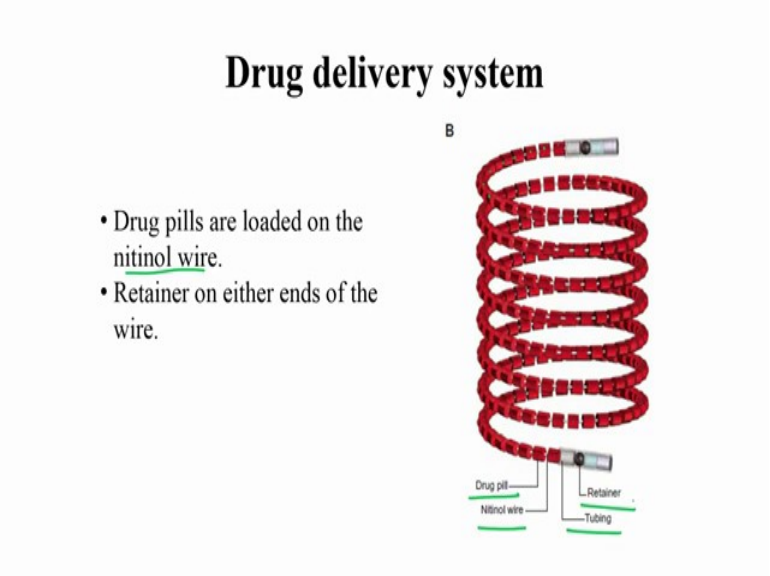

So, one of the methods that these authors chose was a system like this where they have a nitinol wire and this nitinol wire is threading these a small units of tablets, that are threaded through this nitinol wire, you can call them drug pill if you like. So, here it is defined as drug pill, and then towards the end of these the two ends have a tubing and a retainer. And will come to that in a moment what these two things are.

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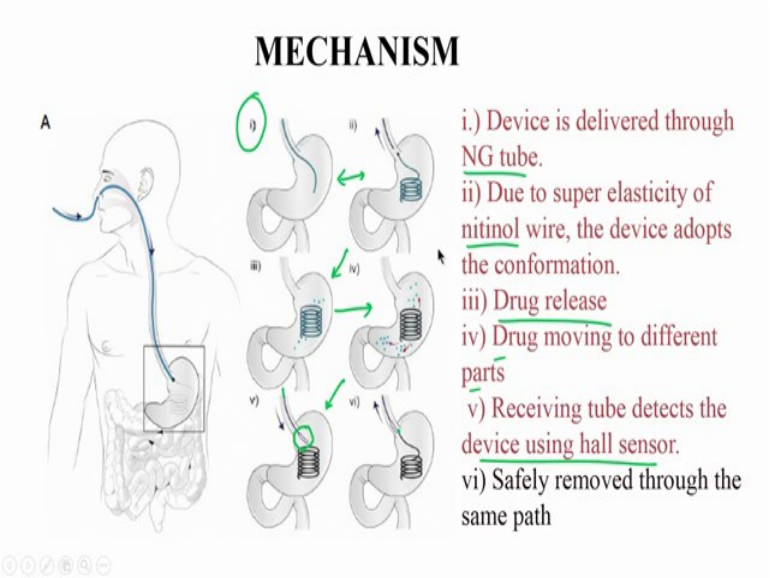

And the whole envision for this is that the device will be delivered through an NG tube. So, through some nasal tube, you thread the device through the oral route through the

esophagus. Once the device reaches the stomach the device at that particular environment will start to coil. So, as you can see this is coiling. So, this is delivery, this is change of shape here, from here you go here where the drug is starting to slowly release and go into the system which is being continued here and once you are done with this, the idea here is you come back with another procedure, you again thread a tube which contains a retriever which will then bind to this device and pull it off. So, this is the major thing.

And they have used nitinol wire because its super elastic. So, it can go through this transformation several times and it will maintain its elasticity, so that means that the device will adhere to the conformation that you have designed it for. It can do drug release at the step 3, the step 4 is only showing that the drug is moving to different parts of the body. And then those retainers that we talked about towards the end those will be used to use as a sensor, so that when you come with another tube they can then detect these retainers and the retainer will bind to the ends and once it is bound to the end it can then be removed out through the same path as it was put in.

So, due to all this what will happen is you will only have to do the procedure twice, one time you will put it in hopefully it is going to release for 6 months and then you can take it out and so the patient will only have to undergo two procedures rather than taking hundreds and hundreds of tablets for a duration of 6 months.

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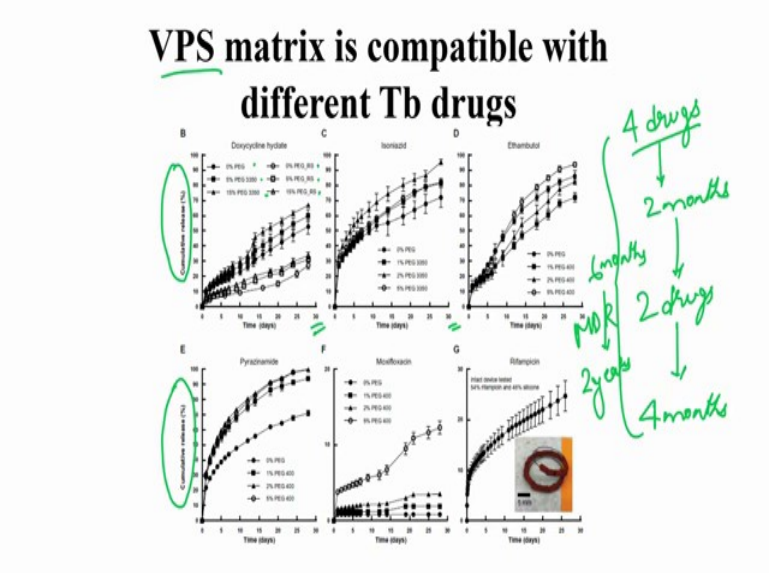

So, here is basically what they are showing is the matrix that they have used, the VPS matrix, and will come to it in a moment as to what exactly this is, but this is compatible with all kinds of TB drugs. So, in TB we have 4 drugs that are typically given, and so these 4 drugs are given for a period of 2 months these are first line drugs, and then after 2 months this is reduced down to 2 drugs which are then given for a period of another 4 months.

So, this is in a case of a standard TB patient. But then there is also drug resistant TB so that means, that some of these bacteria have resistant to 1 or 2 of these drugs. So, in that case this therapy instead of going down for 6 months this can go all the way up to 2 years in cases of MDR. So, that is essentially what is being shown here and this is now showing that in this particular system, the authors in this study were more focusing on getting it to release for up to a period of a month or two.

So, here they are showing with changing the different formulation of these drug pills. They are able to change the release rate and also let it release over a period of 30 days, and all kinds of drugs are compatible with that. So, here you can see the y axis is the cumulative release percentage. So, once it reaches 100 percent that means all the drug is released and you can see in all the cases the 100 percent drug is not released even after 30 days. So, the system is fairly compatible with that.

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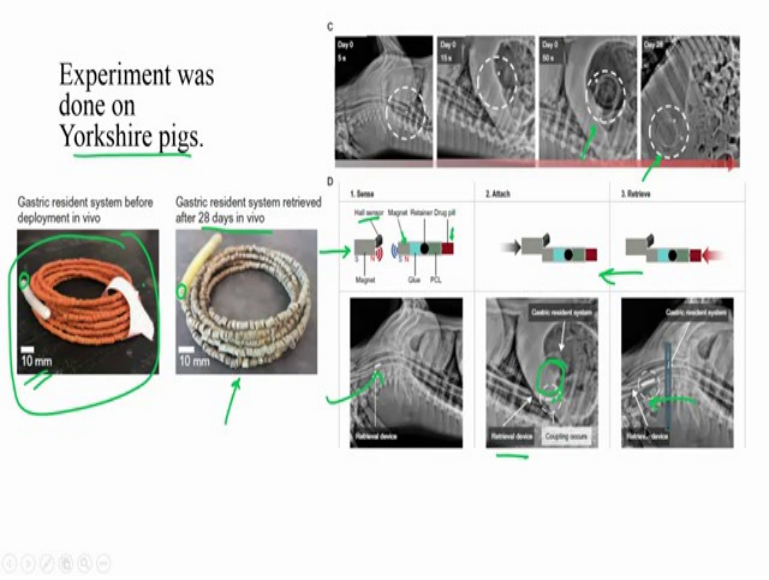

So, then they went ahead and did an experiment on again the Yorkshire pigs as we discussed previously it is a good model. They are similar weight as humans and specially their gastronomy is very similar to human gastronomy. So, so here is a particular implant that they put, just for the scale they have put a 10 millimeter scale bar and this is what they get after retrieving it 28 days after putting in the pig. So, you can see that the device even though it looks fairly discolored at this point it has maintained its shape as well as the whole of the device was retrieved.

And here you can see. So, they have done imaging in the live animal and here you can see this is residing at day 0 how this is going at the time of the procedure. So, this is describing how this looks at the time of procedure and by 50 seconds you see that the device is completely retaining its shape, to what you expect it to look like and then the same shape can also be seen 28 days later in these pigs. And here is describing the mechanism of how this is retrieved.

So, what do you have is at the end of the device, so here a drug pill is ending. And then what you have done is you have put a magnet at the end of this portion and this magnet acts as a sensor. So, you can use a hall sensor which will bind to the magnet fairly strongly and then you can come in with the retrieving device you can bind to this part, once it is get bonded you can then push it pull it out and due to the super elasticity of nitinol, it will it will then open up, come out from the system and then recoil again as its seen here.

And this is again imaging in the live animal showing your retrieval drive device is going in, you are going to go somewhere here where the device is sitting. Here you can see, here is the resident system the GRS what they call and here is the end of it, the magnet is binding to the hall sensor with the retrieval device, and then they are showing that this is now being pushed out where the system is coming out.

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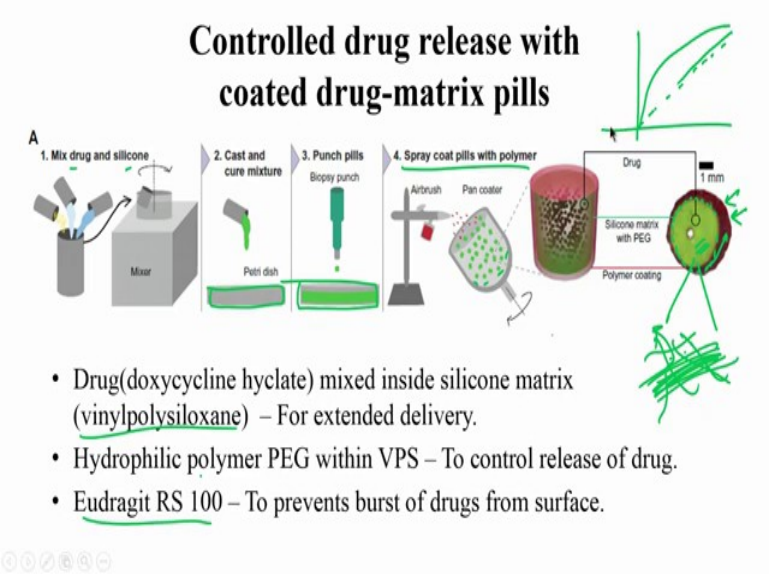

And the little bit on these drug pills that we are talking about. So, in this case, they have a mix of the drug in the silicon. So, you mix these drugs, you make a suspension out of this, you cast and cure it, you polymerize it in a Petri dish. So, essentially it looks like this where you have drug mixed with silicon. At that point you can punch the drug out as to whatever size you want, so you saw the several repeating units in that retrieval or in the GRS system. So, you can punch these out into several of these drug pills, and once you have done you can then spray coat it with various polymers that will act as a coating over the top of this drug silicon mixture.

So, this is how it is going to look like. So, here is your silicon matrix containing the drug. And then what do you have done? You can also put some PEG in it to act as porogen. So if I zoom into this further then I am looking at a very dense matrix and wherever the PEG was it is going to create pores there through which the drugs can then come out.

And then on the outside you can do any kind of polymer coating, you can do enteric coating or you can do some other kind of coating that just to make sure that there is no burst release happening. So, in this case they have used a drug, doxycycline hyclate, an antibiotic this is mixed with the silicon matrix, vinylpolysiloxane, for extended delivery. Hydrophilic polymer such as PEG is then put in to create these pores that I talked about. And then finally, on the top of this on the outside you had the eudragit coating which

prevents the burst release from the surface. So, this coating will dissolve slowly and as it dissolves the drug will start to come out.

So, I hope you all remember the burst release. So, if you have a device and you expect the ideal release to look like this. In most devices what you find is the drug gets released more like this, there is a burst and then the reason for the burst is of course, the drug that is sitting right at the edge of your delivery system immediately comes out when comes in contact with the water. And to prevent that they put another polymer on the on the outside, which does not have any drug and that gives you a more sustained release rather than a burst release.

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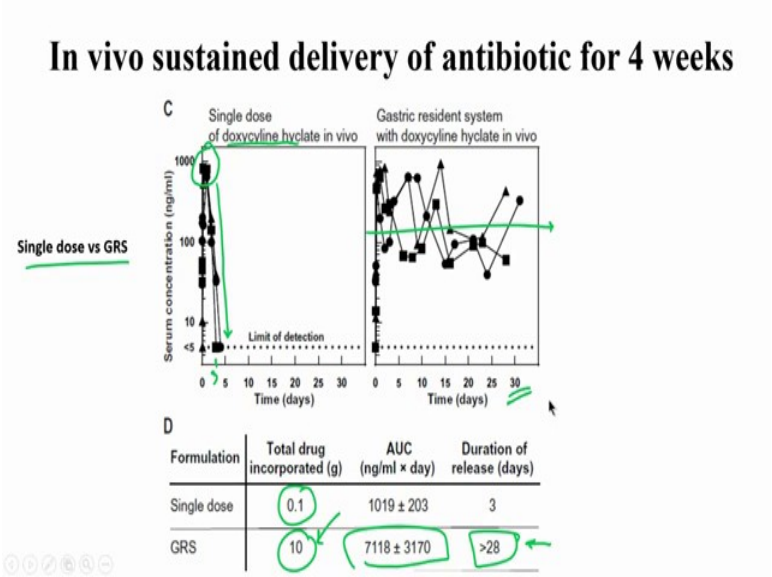

So, here is let us see how it actually does with the antibiotic. So, in this case they have compared a single dose of the drug versus the GRS system, again a single dose with that and, so let us see. So, this is just a free drug, the doxycycline. And, what they see is they have given it orally. So, the serum concentration starts to go up, it reaches very high level all the way up to the 1000 nanogram per ml and then it very quickly drops down. So, by day 2 day, 3 what do you find is whatever you have given is gone. So, now, you have to take more tablets if you want to maintain this concentration.

Whereas, here with the gastric resonance system what do you see it reaches high concentration and then it hovers in that range. So, you can get quite a bit of sustained release over a period of, in this case, they have gone up to 30 days. And again this is just

showing the formulation. So, you have in this case the total drug that was incorporated was 0.1, in this case its 10 gram and you get quite a high AUC as well the duration compared to just the free drug alone (Refer Time: 22:12). So, not only you are able to deliver a lot more drug almost 100 times the drug in a single go it is also getting sustained for quite a bit of time.

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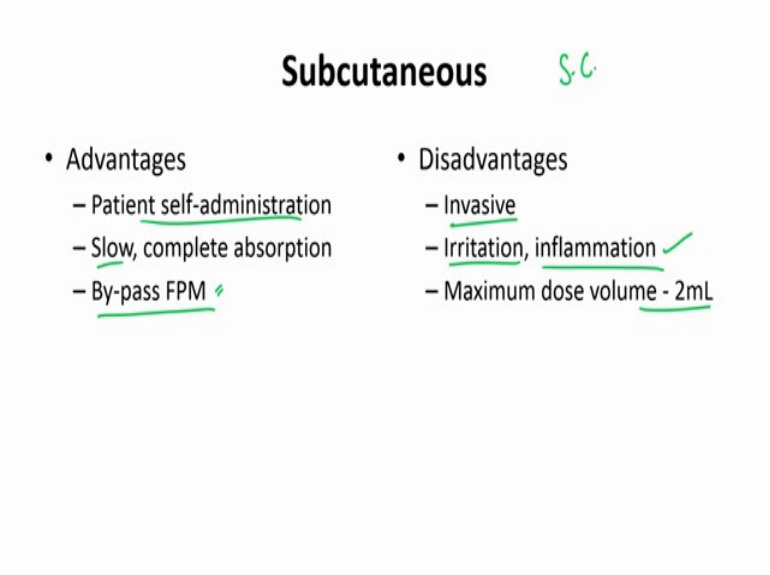

So, we are going to finish the oral discussion now and move on to another form of delivery which is the subcutaneous delivery also sometimes abbreviated as SC. So, if somebody says there is an SC injection that means, it is subcutaneous. And what does subcutaneous? Subcutaneous is an injection just under the skin. So, that is again commonly used, it is actually fairly easy for the patients to self-administer. So, that is one of the advantage, that all you have to do is you can take your skin you can just pinch the skin up put in the injection so that the injection goes through your skin is then free to move and once its free to move you can then inject your drug.

So, it is fairly easy procedure you can design small needles, so that you can actually directly poke like this and deliver things subcutaneously. And, very widely used in research as well as in patients. The absorption is slow and complete, so whatever you have injected has to get absorbed since its already under the skin it cannot really come out and one of the advantage here is you bypass the first pass metabolism. So, unlike the oral route if you eat anything it has to get first of all absorbed through your intestine and

then it will go all through the hepatic circulation, portal vein to the liver where we know that liver is a good organ in terms of metabolizing anything foreign and it is going to make sure that pretty much most of your drug is lost at that point. So, even before you get to a serum concentration you have lost most of the drug in oral route, but this is bypassed in the subcutaneous route.

What are the disadvantages? One disadvantage is of course, it is invasive. So, again you are talking about poking through your skin using some needle, the children, the babies even the adults do not really like it. It causes irritation. So, of course, it will result in some blood as well as irritation at the site, if you continue to do this let us say for therapy demands that you do it every day for 30 days you can imagine how much perforated the site will become and that site will be very irritated, the skin will get damaged. So, all of that it obviously, is a procedure when you are damaging blood vessel you are also causing inflammation to happen, so that is not ideal.

And then there is a limit to how much dose you can deliver; so, unlike the in the oral route where you can deliver hundreds of ml. In this case the maximum you can deliver under a skin is 2 ml, beyond that your skin elasticity will not let it be delivered further, there will be too much pressure as well as you might damage the area in the surrounding.

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So, just an example of this which is out in the clinic. Here is a product which is called bydureon and let us look what it is. So, there is as you can see from the graph itself it

says once weekly. It is an injectable system of 2 milligram dose, subcutaneous use only as its clearly written here. And essentially what it is doing is instead of taking whatever the drug is being delivered every day you can take it once a week. So, let us look at what it is.

So, it is a glucagon like peptide. It is a fairly effective in type two diabetes. So, if the patients are becoming insensitive to insulin, you can give this particular drug, glucagon like peptide which is going to make sure your blood glucose is well maintained and before this product was launched, you needed to inject twice daily.

So, if let us say if I am suffering from type II diabetes I will have to take this glucagon like peptide pretty much every time after I eat something or at the very minimum twice every day. Of course, that is not very ideal because you can imagine this is a chronic disease. So, patients let us say get it at 40 years old and they going to continue to suffer with it till their lifetime; so, for almost 30 years. So, if a patient is suffering for 30 years and they have to take twice a day you are talking about almost 700 injections a year, for 30 years, so that is 7000, 21,000 injections.

So, you can imagine what it will do to the skin site where these are being injected. So, to counter that, this company came up with these devices where these are nothing, but PLGA micro particles that are encapsulating your glucagon like peptide. And you can deliver it once a week. These PLGA particles once it goes under the skin they will slowly degrade and release these drug molecules out in the surrounding for a period of 7 days and then you need to come back again and inject it.

PLGA, we know is a very biocompatible material it will degrade, so it is not like it is going to accumulate over time. So, this will clear out from the body you put another injection with these PLGA micro particles and the patient will have a much better life.

We will stop right here, and we will continue rest in the next class.

Thank you.