Drug Delivery Principles and Engineering
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Lecture – 38
Route Specific Delivery Intramuscular

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

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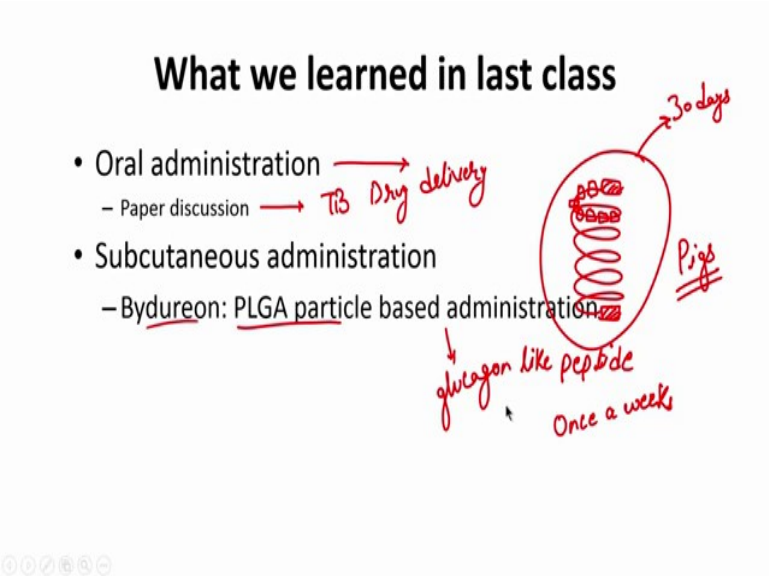

So, we were talking about oral administration, basically talking about how you can deliver drugs orally in a much more efficient way than the traditional ways such as capsules and tablets and in this particular case we discussed a paper that was targeted for TB drug delivery. This system contained of a very large object which basically had a retrieval signal on the ends and made of nitinol wire that contains, drug pills throughout its body, which can be then used to release drug over time. So, the authors of this paper showed that you can actually have such a system, release drug over a period of 30 days. This was the time frame that they tried to test. It could be extended to longer duration by changing polymers.

And they showed a much more sustained release of their drug and much more steady serum levels of the drug which is very ideal in terms of the drug delivery as well as treatment. Of course, this is only been done in pigs, for it to translate to humans, lot more has to be done in terms of safety, in terms of further pharmacokinetics of this drug in humans. But again,

shows a very promising approach of using biomaterials and drug delivery to ensure that the TB drug delivery is much more patient compliant and efficient.

Then we talked about subcutaneous administration; subcutaneous is nothing, but administration under the skin. So, we have a large surface area of our skin. So, that actually acts as a very large reservoir. You can do that at any part of the body and in that we discussed some of the advantages and disadvantages of the system. And we then looked at an example, which is actually already being used in humans. It is a PLGA particle based drug, called Bydureon, which is used to deliver glucagon, like peptide. It is effective for patients suffering from type 2 diabetes, where they have to take 2 injections a day normally, but with this particular formulation they only have to take once a week.

So, almost reduction of 13 administrations, 14 in total and then one administration with this; so, almost per week you are reducing 13 administrations, which improves the quality of the life quite a lot.

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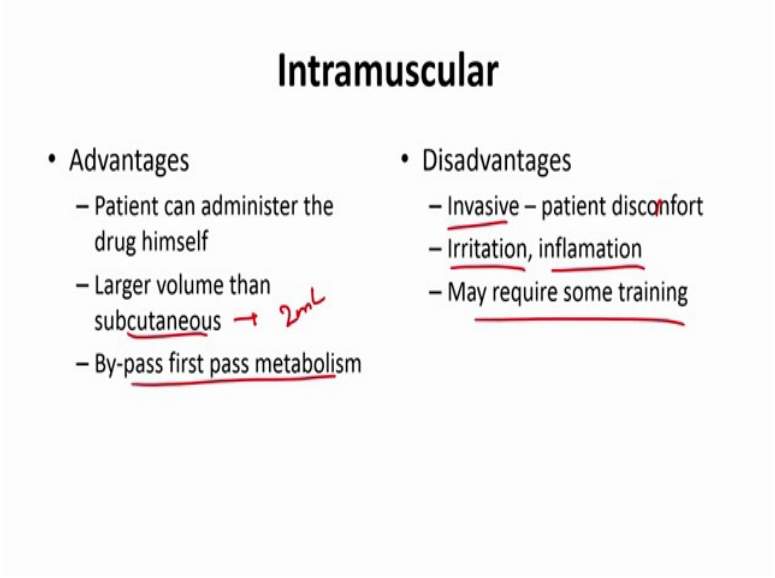

Okay! So, let us move on to the next route that is very widely used which is called intramuscular. Here again some of the advantages are, that patients can administer the drug himself, all that requires is some training to find the right muscle. But humans have quite large muscles in their hips, in the thighs, also in their arms, so those sites can be used to deliver drugs intramuscularly, unlike subcutaneous, you can still deliver larger volumes.

So, we said that for subcutaneous at that the site, you are limited with 2 ml. With something like intramuscular, you can go all the way up to 5 ml, if required, but again it is limited compared to let us say an overall route where you can deliver 100 mls. So better than this subcutaneous right in terms of the volume, but still less and then like the subcutaneous route, it will also bypass the first pass metabolism. So, what is first pass metabolism? It is a metabolism that if we eat something orally most of it first has to go through the liver which is a metabolizing organ and that will ensure that quite a lot of it drug is already metabolized before it can act on it is functional target. So, through both the intramuscular and subcutaneous route, you can bypass this particular metabolism.

So, what are some of the disadvantages of intramuscular site? I will give you a moment to think. So, if you think back to what we discussed in subcutaneous, it is again a very similar sort of delivery. So, again these are some of the advantages, but then it also comes with some disadvantages. So, let us look at them: so first disadvantage lies with subcutaneous is, it is fairly invasive. Again you are talking about the needles being stuck into babies, into children, into adults and nobody really likes this. Again the same problem is that, wherever you injecting this it is going to cause irritation; it is going to cause inflammation and again, that is not ideal.

And as I briefly said that, it may require some training although the patients can administer the drug himself, is not as easy as a subcutaneous or an oral route. You may need some training to make sure that it is actually going into the muscle and not under the skin or not to some organ which is absolutely essential if you want to be consistent with the delivery.

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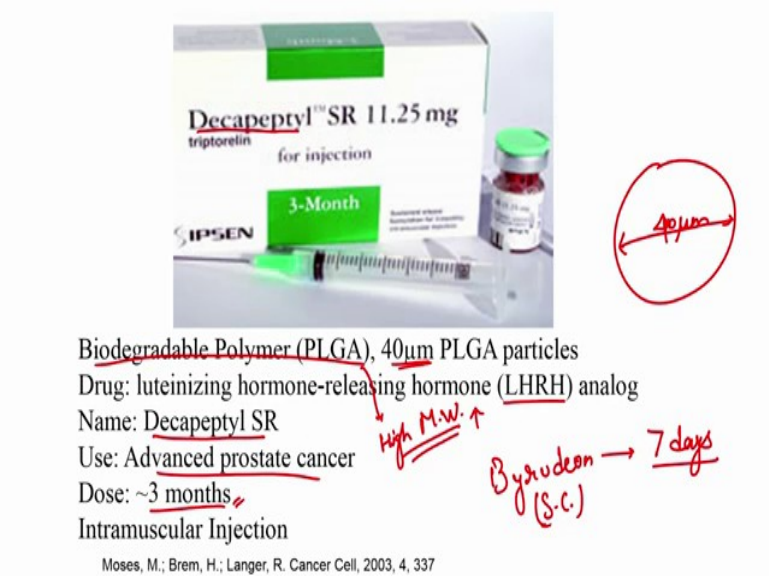

So, let us look at some of the examples that are out there. So, one of the examples here given is Decapeptyl. This is injection which is given once in 3 months and what it is? It is biodegradable polymer PLGA and these PLGA are about 40 microns big. So, the size of them is about 40 microns and they carry a drug which is called LHRH analog, this the more trade names for that is Decapeptyl SR etc., and it is used for advanced prostate cancers.

So, you want to deliver this drug pretty much daily if you are suffering from advanced prostate cancer, but with the use of these particles and use of intramuscular route, you can have this dose go on for all the way up to 3 months. So, for these particles to degrade very slowly, this PLGA must be of very high molecular weight, if we remember what we discussed previously. So, the higher the molecular weight the slower is the degradation.

So, if I now compare this to the other formulation that I told you, this is for the SC route. So, if I now compare this to, what I was saying is going to last in the body for about 7 days, this one we are talking about lasting for 3 months. So, if I have to compare between the molecular weights, the molecular weight for this will be higher right? For this to degrade in about 7 days, this will be fairly low molecular weight PLGA. But in this case it is higher, but this is one of the product that is out in the market, again it is probably debatable that you can probably use this system Decapeptyl in your subcutaneous injection as well. So, it does not really stop you from doing that, but it is currently approved for intra muscular because that is

why the testing is being done, but ideally speaking this, should also work for subcutaneous site.

Although just a word of caution there is that, like with the delivery, the how the body responds to different drugs at different sites can also be different. So some site may be very immunogenic some site may not be very immunogenic. So, if it is recommended for intramuscular it should be used only intramuscularly.

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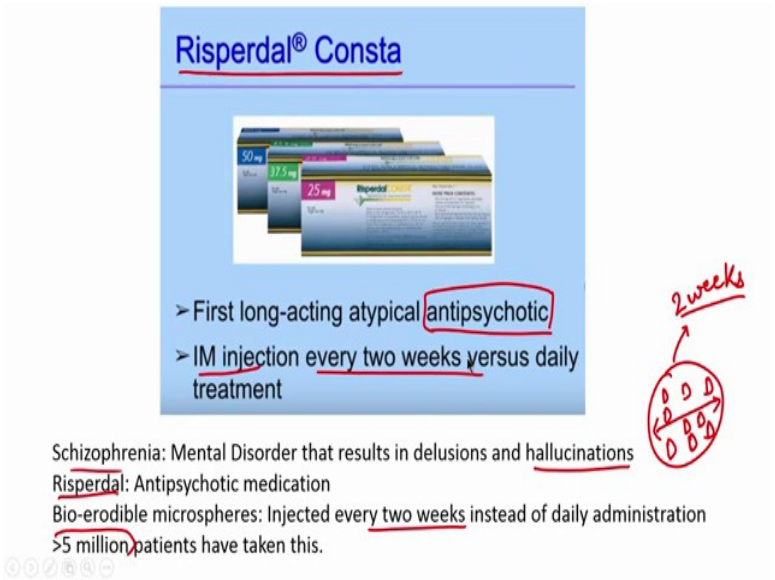

Here is another example. So, this in this case we are looking at Risperdal consta and this is the first long acting antipsychotic that is given. With this type of disease it becomes actually very paramount that patients stick to their dose regimen, because, let us say if a patient is supposed to take the drug every day and the patient do miss that, Because it is related to any sort of brain disorders, the patient may not be even capable of, once they miss the dose, they may not be even capable of then going back and taking the dose maybe their mental state may change so much that they may not be able to do that anymore.

So, that could be a potential life threatening risk, so that is why it is very important for such patients to ensure that they stick to their medication regimen and something that can prevent them from doing it every few hours or every day, would go a long way in improving their patient life. So, this is also an IM injection and this is given every 2 weeks, compared to a daily treatment if you use only free drug and it is used to treat schizophrenia, which is a mental disorder and results in delusions and hallucinations. So, the patients will start

imagining things that are not present and they may start looking at some hypothetical things which are actually not present. So, those are hallucinations and Risperdal is an antipsychotic medication as I just briefly discussed.

And what were done in this particular formulation are the bio erodible polymer microspheres are used again. So, in this case they are saying that their residence time is about 2 weeks, so that means, that these polymers will degrade over a period of 2 weeks and whatever drug is getting encapsulated, in these polymers will then release over that period of time. So, this is injected every 2 weeks as I said and this has actually resulted in almost more than 5 million patients using this. So, this is just a very classic example of how small little improvements and bioengineering can play a big role in improving patient lives by a huge margin.

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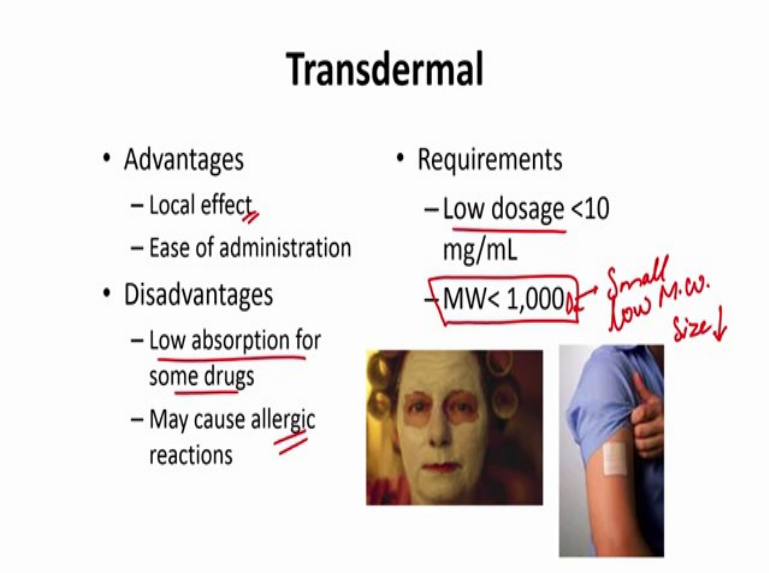

Okay! So, let us talk about the next route which is transdermal. Again as you can see from these pictures this is something that we most of us have basically experienced this quite a bit when we put creams on, when we are putting any kind of skin patches this is nothing, but that transdermal which means through the skin. And some of the advantages of this are first of all it is a local effect.

So, I prevent the exposure of the drug throughout the body. So, let us say if the drug is only on the skin let us say this infection on the skin or some injury onto the skin, I do not really want that drug to go to all parts because all of these external molecules may cause some toxicity, but among all the different routes that we discussed the oral, the subcutaneous, the

intramuscular, all of them result in a buildup of a systemic level concentration This will also result in some systemic level concentration, but predominantly it will be only topical.

So, it will be only local and it is very easy to administer again we never require help of any professional to do this, this is fairly easy however, there are certain requirements for what type of drugs will actually work with this. So, first of all you can only give fairly low dosage because the skin is actually a very good barrier, when it comes to absorption through the skin. So, skin is designed to make sure that we are keeping all the pathogens or the foreign material unwanted material outside our body and that is why it is very difficult to penetrate that barrier and deliver things.

So, first of all very small amount of drug can be given and then, secondly the drug has to be small as well. So, low molecular weight. If the molecular weight is higher, then the size is higher, as only as you decrease the size you can actually think about delivering it through the skin.

So, here are some of the disadvantages I have talked about it: first of all there is a low absorption for some drug. So, even at this size range when you are talking about less than 1000 Daltons, what you will find is some of the drugs have less permeability through the skin just because maybe there are other properties that are not ideal: maybe they are ionic, maybe they are hydrophobic; depends on the drug in the application you are looking at. But their absorption will also be different and of course, the skin is actually fairly immunogenic organ.

So, if it is something that the body does not like and the immune system starts reacting against it, you can have lots of inflammation and allergic reactions happening. So, that is of course, not desirable. We know the skin is very prone to the immune system reaction because, even if we, let us say rub our skin, what will find is, it becomes red which basically tells you that the immune system is activated in that local area and trying to look for any kind of pathogen or foreign material.

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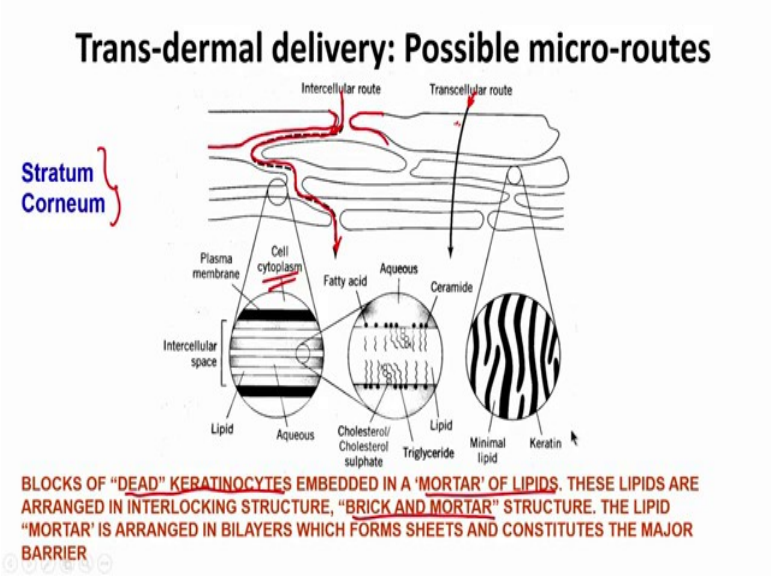

So, let us really look as to what is the skin? So, the major barrier there through the skin is a layer called the stratum corneum and what it is? It is a layer of dead cell. So this is basically the zoomed in image of the skin: what do you have is various cells that are lined and for a solute molecule to go through your skin cells, it has to take one of the two routes.

Either it has to find the gaps between different cells and traverse through that gap or it has to either go through the cell itself. So, it has to be lipophilic enough to be able to interact with the membrane, but still be amphiphilic enough to be able to then also interact with the cytoplasm. So, these are the 2 major routes and both of these routes because the skin is very tightly packed in terms of the cells, creates a limitation as to what is the amount, as well as what is the size of the drug that you can deliver.

So, as you can see here, this is what is represented and the way the skin works is there is a dead layer on the top. So, dead keratinocytes, which are acting as a mortar of lipids so; that means, that anything which is hydrophilic is not going to be able to penetrate much through the skin because this lipid layer is not going to like it. So, to be able to penetrate through the lipid layer it has to be hydrophilic sorry, hydrophobic and again these lipids are then arranged in some interlocking structure. So, that is why their brick and mortar structure is there.

So, as you can see here there sort of interlocking with each other and once it goes through this lipid layer, then it has to travel through the cells as well. So, there is cytoplasm that the drug will need to travel as well and because of that the extremely hydrophobic compounds

will also not be able to go through. So, it has to have some amphliplicity to it. So, that can interact with some solubility and some interaction with the aqueous phase as well.

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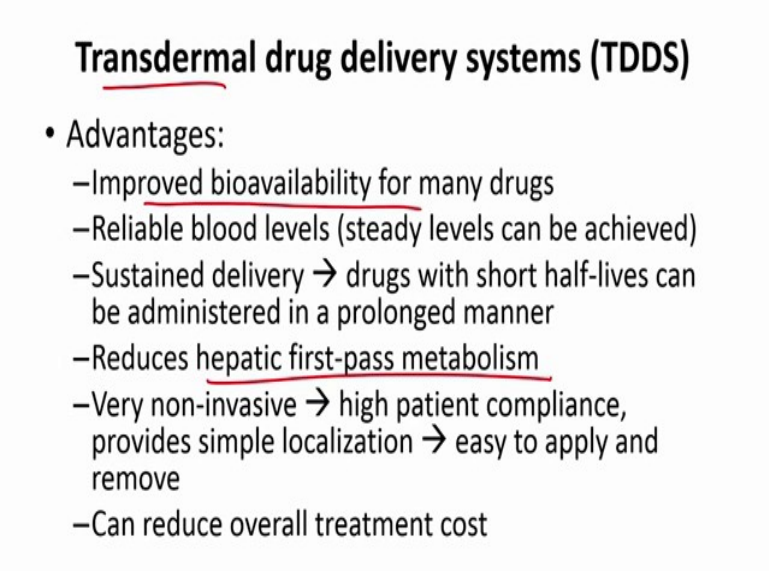

So, again some of the advantages here are you can, if you can deliver something transdermally, you can ensure a good bioavailability for many drugs you can have very reliable blood levels can be achieved if you can do a transdermal delivery and then you can also have sustained delivery. So, what you can do is you can put a patch and let us say if that is able to deliver a particular drug transdermally you can continue to fill the patch and that will ensure that the drugs have very short half life, maintaining a certain concentration in the serum.

Again, there is no first pass metabolism; the drug will have to go through. So, that is an advantage unlike in the oral route similar to what subcutaneous and intramuscular, you do not have to go through the liver at the very first in the very first go. So, these drugs have chance to interact with various targets before it reaches systemic circulation and goes through the liver. It is very non-invasive, it is very high patient compliant, all it is just application of either a patch or some cream provides localization and it is very easy to apply as well as remove. So, if you do not like it of it is causing adverse reaction you can easily remove it, unlike your intramuscular, subcutaneous route where once you have injected your particles they are there. You cannot really remove them anymore you can only inject more, but once it goes into that system you cannot remove that, but here you are much more control. So, it

since it is over the skin, you can easily remove it and of course, is since the involvement of the health care centers is much lower here you can reduce the overall treatment cost as well.

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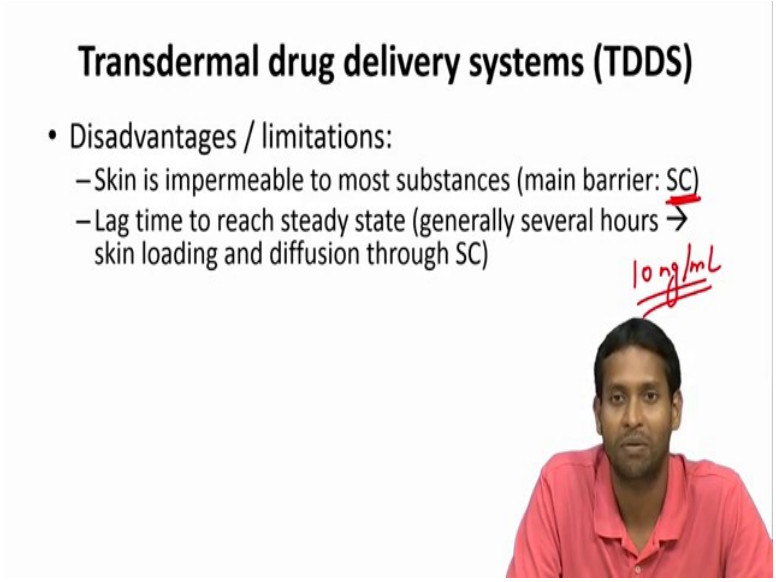

So, some more things. Let us talk about some major disadvantages. So, we briefly discussed about this already the skin is impermeable to most substances and the main barrier is that stratum corneum layer so, pretty much 90 percent of the things that you want to deliver, 90 to 95 percent of the things will not be good enough, to go through the skin. So, there is a quite a bit of lag time, before it reaches steady state, so even if, I let us say put a patch right now there could be few hours before it reaches a concentration in my blood because the diffusion is fairly slow, that it reaches the steady state.

So, again if I say that a drug has a serum level requirement of 10 nanograms per ml. So, to be able to build up this concentration in serum I have to deliver quite a bit of drug and that may take few hours. So, if there is something that I want immediate relief, let us say if I am suffering from lots of pain and I want some painkiller, I cannot really use this route because the patient will not be very happy suffering from the pain for more than few hours.

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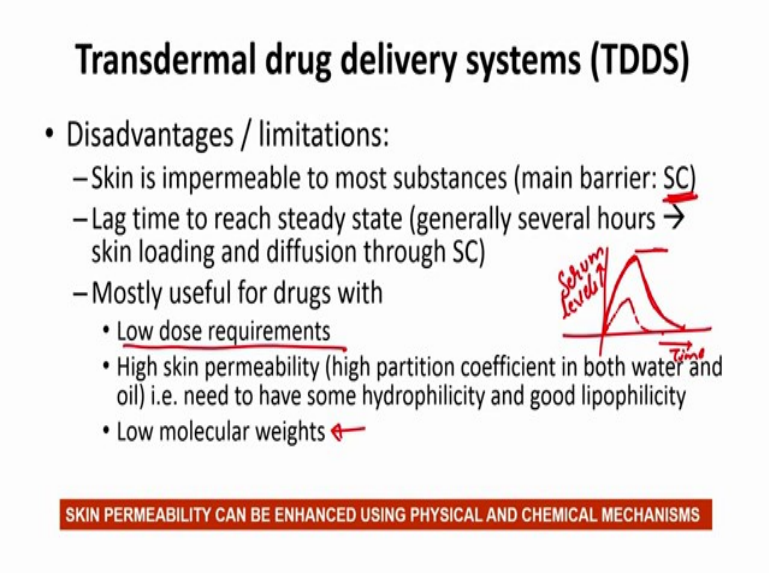

So, this is one of the disadvantages, again we discussed it briefly is, first of all only allows low dose requirements. So, you cannot really build up a whole lot just because the diffusion is slow and the clearance can be actually faster than your build up. So, typically what you have seen is let us say, if I inject something subcutaneously or intramuscularly and I measure the serum levels, this is with time. So, what do you typically see is something like this and what it showing here is, because whatever site you have injected it is taking time to diffuse into the blood and then while it is also doing that the body is also clearing it slowly. Maybe it is metabolizing as well as it maybe it is excreting it out through the urine and hence it starts to go down.

Now, what we are saying with the skin is, this absorption is very slow. So, now, you are essentially talking about something, that is going to take much slower; however, because it is that slow the clearance then starts to dominate. So, maybe you have injected the same amount, but what you will see is the serum level may only go something like this. So, if you want something to reach a certain concentration which is high, it may not be possible with the transdermal delivery.

Another disadvantage is, there is a high skin permeability: that it needs to have some hydrophilicity and good lipophilicity as we just discussed. So, for any drug to have high permeability it needs to be amphiphilic. So, then that puts a requirement of only maybe the drugs which are amphiphilic can go through and you may not be able to deliver all kinds of

drugs. So, as I said only maybe 5 percent to 10 percent the drug that you are exploring can go through the skin and then even after that it has to be low molecular weight because it needs to go through several barriers and the large molecules will not be able to diffuse through those.

However having said all that there are now experiments and there are literature suggesting that you can enhance the skin permeability through various physical and chemical mechanisms. So, those are feasible and let us see what you can do.

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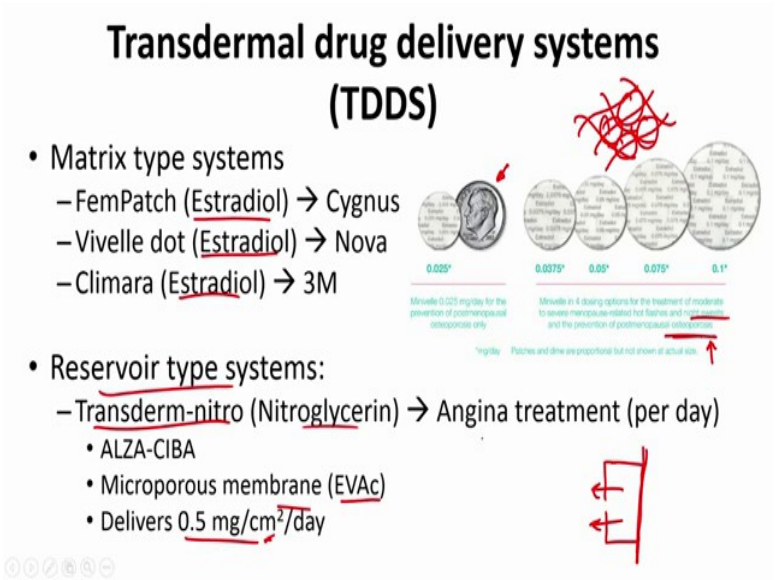

So, before that a couple of examples; so, in this case we are looking at some matrix type system that I used. So, these are various systems to deliver Estradiol, which is nothing, but a growth hormone. What you are looking at is, these skin patches you can see here is a quarter for just for the size comparison and you can get different sizes of this you can patch it over your skin and these are matrix type systems. So, if you remember, a system which look like this, drug is slowly diffusing out from these matrices and as it touches the skin it starts to diffuse in and essentially builds up the concentration.

So, it is a much sustained release; however, the absorption is slow, but then this can be used over a period of months and in this case this is used quite a lot for post menopause. So, typically women suffer menopause anywhere between 45 to 50 years of age and what that does is it makes them for the further susceptible to a disease called osteoporosis. They can also have night sweats, all of which makes their bone weak and now that the bone is weak, this enzyme sorry! Then this hormone then acts to make sure that the bone is not getting

weak and weak. So, that they may start suffering from fractures, we discussed about osteoporosis already remember? So, this particular hormone will ensure that the bones are not getting weak very quickly and these women are then not susceptible to fractures.

And then we also have reservoir type systems. So, very similar concept here, but instead of being matrix you have some sort of a reservoir, where maybe there is some semi-permeable membrane on one side and then an impermeable membrane on the outside and that can also help you deliver things. So, these are again micro porous membranes various systems are out there (Refer Time: 24:38) of EVAc is been able to deliver about 0.5 milligram, per centimeter square per day.

So, it is very well defined. So, let us say if I need 1 milligram dose then I will put two of these or I will put a patch, which is about 2 centimeter square in area and that will give me enough of the drug and in this case this is the drug which is being used is Transderm nitro, which is nitroglycerin and is used to treat Angina.

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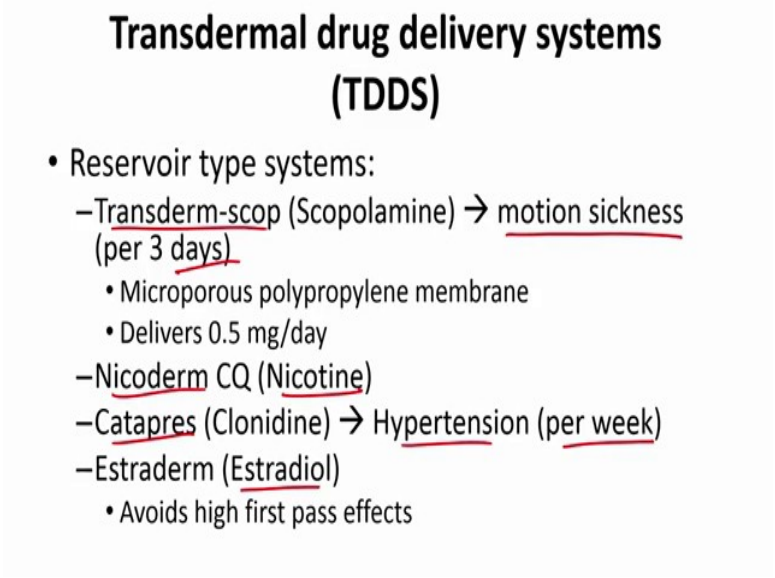

So, let us talk about some more reservoir system. So, there are other examples as well there is a Transderm Scop which is nothing but it is something to prevent motion sickness. So, lot of people suffer from motion sickness where if they are let us say in bus for quite a long duration, they may start to feel nauseated and sick and so to treat that the drug is given. So, this could be over a period of long durations. I mean if somebody's traveling let us say from

north of India to all the way to south of India in buses or trains it may take up to 2 to 3 days for them to travel that.

So, these patches then become very useful. So, they can put these patches on their skin and this will be effective for about 3 days and that will help them not feel nauseated and be healthy during the travel.

Then there are other, there is Nicoderm which is delivering nicotine, used by patients who want to leave smoking. So, you can slowly go away from smoking by using these patches. Then there are other examples for hypertension, another example is Catapres this is given per week. So, quite a long duration you can use it for and then we already talked about Estradiol, but they are also available in reservoir type systems as well. We will we will stop here I will continue rest in the next class.

Thank you.