Drug Delivery Principles and Engineering
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Lecture - 39
Route Specific Delivery Transdermal – II

Hello everyone. Welcome to another lecture for Drug Delivery Engineering and Principles. Let us quickly recap of what we learned in the last class. So, at this point we are talking about a module which is on what route to choose for various applications. And we have discussed few routes already and we have continued that discussion today's class as well.

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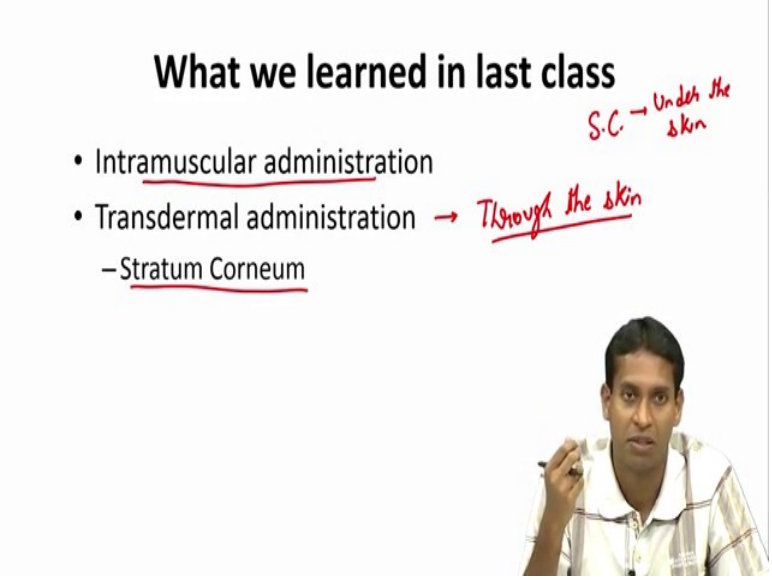

So, in the last class we basically focused on the intramuscular administration where what essentially that means, is the drug is injected into the muscles. This could be large muscles such as thighs, biceps, hips. So, this is some of the common routes you might have seen even for children this is a very widely used route.

And some of the advantages of this route are of course, patients can self-administer with little bit of training. It is whatever you inject 100 percent of it goes their absorption is fairly fast. However, there are some limitations that first of all there is needle involved, so this irritation and patient compliant is low. So, we discussed all those factors and then we discuss how we can use another route which is transdermal administration and that is

nothing, but injecting under the skin or through the skin in this case. So, this is through the skin.

And this is in terms of the delivery it is similar to what you had learned for subcutaneous the SC injections, but in SC injections you were then we need under the skin. So, this is under the skin which means that the needle was penetrating right through the skin whereas, in cases of transdermal delivery, you are still penetrating the skin, but not throughout. So, you are injecting somewhere in your thickness of the skin. So, that is one of the routes that we were discussing last time.

We discussed the one of the major barriers for anything to diffuse through the skin is the stratum corneum. So, ideally what we would like is if you apply let us say a cream or some liquid on your skin containing the drug that should be able to go through the skin and go to the systemic delivery or to the site of location you want, but it is not really very feasible just because the skin is a very good organ in keeping things out it. The main purpose of the skin is to protect us from the external environment and so this act as a very tight interface where it does not let anything pass through it very easily.

And the major reason for that is this layer called stratum corneum which is nothing, but a layer comprised of lots of dead keratinocytes arranged in a very zig zag and lock fashion which does not let large molecules, charged molecules to pass through its very heavy in lipids as well. So, for any molecule to pass through those molecules have to be slightly amphiphilic for that. So, that they can pass through the lipid layer as well as, then they can go through the cytoplasm as well.

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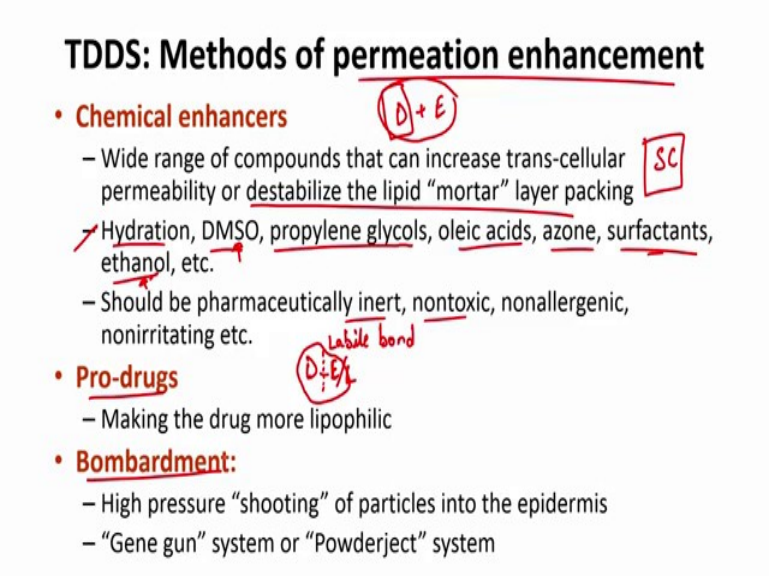

So, let us talk about more. So, this was so far what we talked about is something that has traditionally been used, so applying creams and all or maybe even needles. In this part of this topic will discuss what are some of the research base advancement that has been made that can go to the clinic and also actually give us a lot more control over this delivery as well as efficiency.

So, what we talk about is permeation enhancement and the word is self explanatory where permeation is nothing, but permeation through the skin. So, how can we enhance that? So, along with the drug what we can do is, we can give some chemical enhancers. So, maybe your drug D gets added to some enhancer E and that causes a much higher permeation of this drug D through the skin. So, that will allow you to monitor your dose as well as increase your dose.

And in terms of chemical enhance a wide range of compounds are used that can increase transcellular permeability, the whole concept here is used some chemicals that will destabilize this lipid mortar layer present in the stratum corneum. And once this lipid layer gets destabilized or gets removed the permeability of the drug will increase in a dramatic fashion because as we mentioned before a stratum corneum is the layer that is responsible for quite a bit of protection from the drug to permeate through the skin.

So, that is essentially the whole concept of most chemical enhancers that are used in the field. And there are quite a bit of them, one is simple hydration. So, if you instead of

keeping the skin dry if you hydrated, it helps in an aspect not by a whole lot, but some. DMSO an excellent enhancer where DMSO is a quite polar solvent and its able to interact with the lipid mortar layer and able to somehow destabilize this layer packing which then, so if you give a drug with a DMSO, it will result in quite a lot more enhancement through your skin.

Then there are some polymers that are used. You have polypropylene glycols you have oleic acids, azones and surfactants. Surfactants are again will be very good because as we said surfactants can interact with both hydrophilic and hydrophobic components and that can result in quite a bit of enhancement. Then ethanol itself is a very good permeable molecule through the skin as well as it can also enhance the delivery so in fact, if you the one form of ethanol penetration is through the skin.

So, if you are dealing if you are working in a job in which you have to touch ethanol quite a lot you can actually get that ethanol levels so high in your blood that you might even get intoxicated. So, all of these molecules are used for enhancement of permeation of the drug that you are looking.

The one thing that you need to be careful about is the safety of these molecules. Again, by definition, since these molecules are taken and are able to destabilize a lipid layer, most of our live cells are also made up of lipid layers. So, they can be fairly toxic, like something like DMSO, if you end up consuming it or if its buildups too much concentration in your body, that is never good. Same thing with other kinds of surfactants and ethanol as well. So, just need to be careful with that the safety.

And then not only that even if let us say it is not building up too much level even if let us say you are putting it on a small patch of your skin the problem there is you have to make sure that that area is then sterile and is maintained sterile for few hours, because what you have now done is you have destabilized this lipid mortar layer which was obviously, essential in protecting you from foreign pathogens let us say there are viruses bacteria, fungus in the air.

At this point since my skin is well intact, they cannot really go through, but once I have used these enhancers, they have now caused my skin to be not very intact and so not only for the drug my skin is now susceptible to higher permeation for all these pathogens as well. So, got to be very careful it should be pharmacologically inert obviously, should be

non toxic it should not really cause the allergic reactions,7 if the immune system gets irritated that will be another problem which then patients will not likely to use any such enhancers. So, those are some of the things that need to be taken care about.

Then we can go back to prodrugs. So, this was just simply mixing that to enhancer in the drug. You can actually link the enhancer with your drug with some sort of a labile bond and then this can be used to deliver. So, because now you are making the drug more lipophilic in this particular case, this lipophilicity will cause the drug to move much faster across the skin and in a much more efficient manner, but then eventually you do not really want this enhancer to be present right till the end and in this case this enhancer could be just moiety that makes it more lipophilic. So, you add this very similar to a prodrug concept that we have talked about.

So, maybe you add a bond which is an enzyme sensitive bond, up regulated in a disease or maybe this is just something that constantly present in our body. So, you put that in here once the drug reaches the site of its action or at least crosses the skin barrier, this bond get degraded and then the drug is free to move around and act on whatever target it was supposed to act.

And then finally, you can use some physical method. So, in this case its written as bombardment. And what you can do is you can come up with high pressure particles that shoot into the epidermis. These are again we are talking about micro, nano sized particles. So, they are not, they are not actually causing a pain to your skin or to yourself, but what they are essentially doing is poking little very minute holes.

There might be some pain associated with it if they touch the pain receptors and the nerve cells, but in that way what you can do is now you have created these holes which are going to be transient obviously, the skin will heal itself very quickly. So, you want to ensure that in that right before you apply your drug you shoot them with all these bombardments and then you can come in and put your drug in there which is going to enhance the permeability because now the stratum corneum is not even present there is a hole in there. So, that can increase the efficiency by quite a bit.

Again, this is a very dangerous method. Several reasons, because first of all now you have exposed the skin to external micro environment, where all these bacteria, fungi will be able to also access your is your skin and be able to penetrate further inside. And then

secondly, it can cause pain. So, maybe it might not be patient compliant. And then there are other systems like gene gun very similar concept - powderject system that you essentially just bombard with some mechanical forces, you are causing the disruption on the skin to happen.

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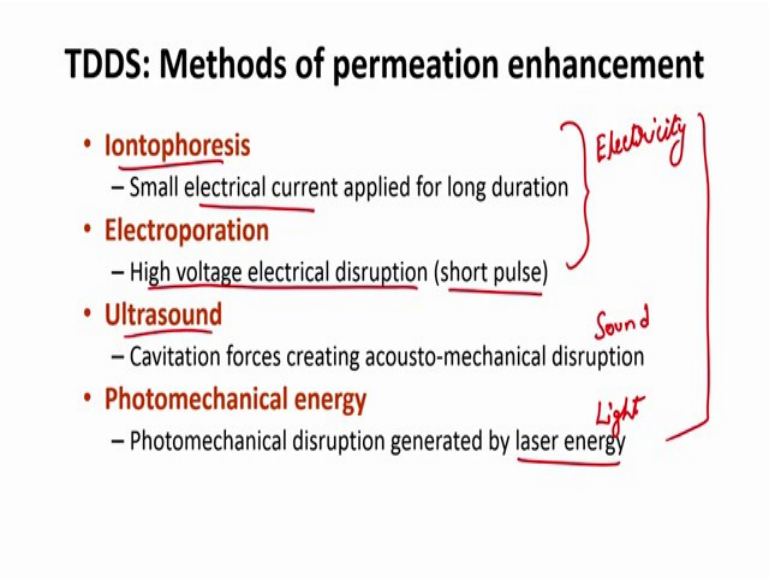

So, let us talk a little bit more. You have another method which is called iontophoresis. And this is a more recent method that has come up. And in this what you are doing is you applying a small electrical current for long duration and because this small electrical current is applied, the layer gets destabilized due to the movement of ions and all these lipids also get charged they move around, so there are interlocking pattern that was preventing the drug from going through is disrupted and now the drug can essentially go through these channels that are formed due to the application of electric current for long duration. And these electric currents are fairly low in terms of the voltages. So, it is not like it is going to cause shock to your body. So, it is well tolerated by the patient.

Then there is electroporation, in this case you are applying a high voltage to cause electrical disruption but for a very short duration. So, this is going to cause a little bit of pain to the patient, but it is for such a small duration that the patient does not really feel much of it. And again the concept is the same, because of this electric current either long duration for short electrical voltage or short duration for high electrical voltage, you are

going to cause the destabilization of the mortar layer in the stratum corneum and that is going to increase the permeability by quite an amount.

Then there are more financial systems you have ultrasound. So, this is sound based. Essentially you send these acoustic signals onto your skin and these sound waves then cause mechanical disruption to happen and causing cavitation in that area, which then can essentially increase the permeability of whatever drug you are looking at. So, essentially all these methods that we are discussing so far for the permeation enhancer rely on the fact that somehow, we need to disrupt the stratum corneum layer, and immediately before it heals itself, which again the skin has a very good healing capacity. You have probably already seen that, if you get a cut the blood actually stops within few seconds and then within few hours you have actually completely sealed of skin there.

So, it is a very good capacity. So, what you are essentially doing you are using this property of the skin by disrupting the skins because you know that it is going to heal itself very quickly, and then applying the drug for that little bit of duration let the drug go through and because the skin will heal very quickly you do not have to worry much about how different pathogens may go in if you keep the area and sterile environment.

And then another way very similar is the laser-based method. So, you can use these photons generated by the laser to cause disruption again this was on the basis of sound, this is on the basis of light, these two are on the basis of electricity. But, the common theme here, is all of them are disrupting the stratum corneum and causing the drug to enhance its permeation.

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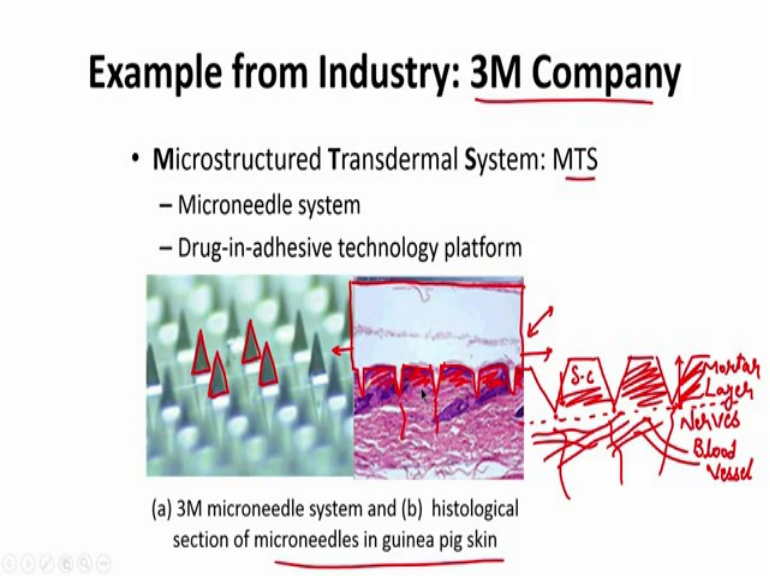

So, let us take a look at some examples here. So, this is an example from industry. 3M is a one of the major companies in quite a bit of products including transdermal products. And what they have done is : this is a different kind of system now. So, what they have done is they have designed the system which we call MTS which is microstructure transdermal system. And what it is? It is a series of micro needles. So, if you can see this picture which is focused on this region, but there are several needles that you see here.

So, these are nothing, but these are micro needles which are arrayed on let us say a silicon wafer or any small plastic tube, and this is how and in this case what you are seeing is now here is the plastic mold on which these micro needles are all set up right. Obviously, I am showing this area, but it is going to be in all two dimensions in this dimension as well as in the in the dimension going back and forth. So, essentially this dimension and. What is the concept here? The concept here is: patients do not like needles because needles cause pain, it is not very patient compliant. So, why do not we remove that pain? And so, what they observed and they are not the first one, a lot of people observe this they are the one who marketed this.

What they observed is that, in the skin the actual pain network the nervous system the neurons and all the nerves lie much below the skin, so that, if I say that this is the skin this is the starting of the skin here is your stratum corneum, and then as you go further down you have these nerves running through your skin, nerves and blood vessels. So,

you have nerves and blood vessels always go hand in hand. So, what is being utilized is this gap that is present from the top of your skin to the nerves in the blood vessel layer. So, let us say this is it. So, unless my needle actually touches the nerve, I will not feel the pain because nerves are the one who tell our brain that there is something touching that is what the gives the sensation of pain. So, there will be no pain unless the nerves get activated.

And so, if I design a needle which actually only just comes up to these regions and not really go beyond this, so what I am essentially doing is I have traversed this mortar layer. So, the mortar layer is this. So, I have traversed this mortar layer which is the major blockage for delivering things and so here is all your mortar layer and I have now traversed this.

So, the permeation that was getting blocked majorly through this layer is no longer applicable and once the drug is getting released at these heads the drug can very easily permeate and diffuse into a system. So, that is the whole concept with this. And so, that is what they are showing here. So, this is that initial system and this is they are showing that a section of a micro needle in to a guinea pig skin.

So, as you can see these needles have sort of embedded themselves into the skin and if something gets released now, the initial layer which was fairly impermeable is not going to be able to have any effect on that diffusion. So, this resulted in quite a bit of enhancement of your delivery.

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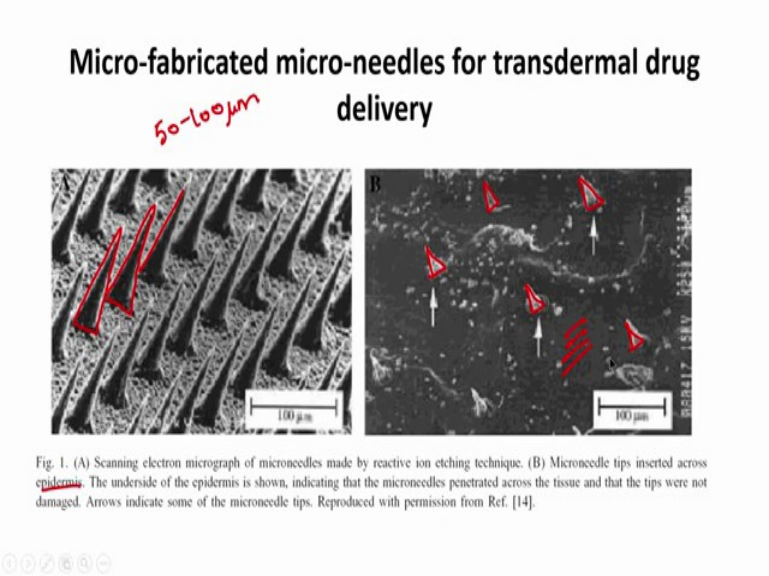

Fig. 1. (A) Scanning electron micrograph of microneedles made by reactive ion etching technique. (B) Microneedle tips inserted across epidermis. The underside of the epidermis is shown, indicating that the microneedles penetrated across the tissue and that the tips were not damaged. Arrows indicate some of the microneedle tips. Reproduced with permission from Ref. [14].

So, here is some more images here. So, this time we are looking at a SEM micrograph of these micro needles. So, again here is a side view and you can see several of these micro needles, and if you look at the scale bar, we are talking about the length of these micro needles from anywhere between 50 to 100 microns.

So that means, that up to 50 100 microns, which is the major thickness of your stratum corneum you can diffuse that through and here on the part b, what you are seeing is these micro needles being inserted into the epidermis and then you are looking from the other side. So, what you can see is these needles is just poking out from the skin. So, again clearly showing that this lipid mortar layer is being able to easily penetrate through and you have much better delivery of your molecule.

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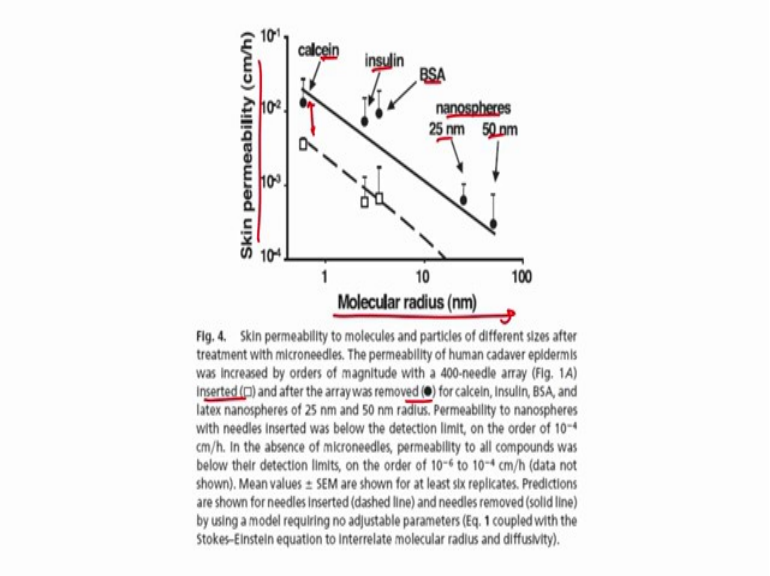

Fig. 4. Skin permeability to molecules and particles of different sizes after treatment with microneedles. The permeability of human cadaver epidermis was increased by orders of magnitude with a 400-needle array (Fig. 1A) inserted (□) and after the array was removed (●) for calcein, insulin, BSA, and latex nanospheres of 25 nm and 50 nm radius. Permeability to nanospheres with needles inserted was below the detection limit, on the order of 10^{-4} cm/h. In the absence of microneedles, permeability to all compounds was below their detection limits, on the order of 10^{-6} to 10^{-4} cm/h (data not shown). Mean values ± SEM are shown for at least six replicates. Predictions are shown for needles inserted (dashed line) and needles removed (solid line) by using a model requiring no adjustable parameters (Eq. 1 coupled with the Stokes–Einstein equation to interrelate molecular radius and diffusivity).

And here is some of the data for that. This is the skin permeability value. And so, what do you; what do you see here is basically, you have different molecules like Calcein, insulin, BSA, just some of the model molecules even some small nanoparticles? And what you are trying to see is whether you are skin permeability is increasing or not. So, you have these empty squares which are nothing, but when you have inserted the array and you see that the skin permeability is fairly and almost an order of magnitude low, but once you have used these micro needles, your skin permeability has increased for all of these molecules, by quite a bit amount. So, that way you can and this is for various radii as I was saying.

And so, you can increase the skin permeability by quite a bit amount using this method compared to the enhancer's method talking about, they would usually only give marginal increase by let us say two fold, three fold here you are talking about an order of magnitude that has a increased.

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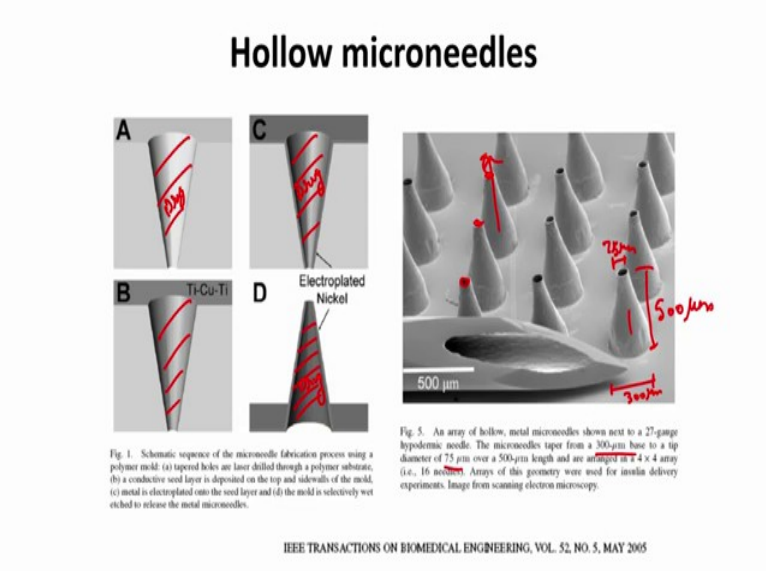

And so how would the actual delivery happen through these micro needles? So, you can make these micro needles hollow and you can fill up your drug in this compartment, all of this compartment can actually have your drug. And this is basically showing one of the type where we had titanium and nickel were being used, but you can make it from other materials as well. And because of these holes you can even cap these holes with some let us say water soluble polymer. So, once it comes in contact with the body this is going to get dissolved away and then the drug can diffuse out from these holes. So, that is the major concept here.

So, in this case you are basically seeing micro needles with the taper of three hundred microns to a tip diameter of about 75. So, basically what they are saying is this is 300 microns, this is 75 microns, and so, you have quite a bit of space to which to fill and this is of course, 500 microns. So, you have quite a bit of space to fill this in and not be able to worry about the amount of drug and not only that you have this is just one pillar, but you are several of them. So, you can actually load quite a bit of drug and permeate it through the skin.

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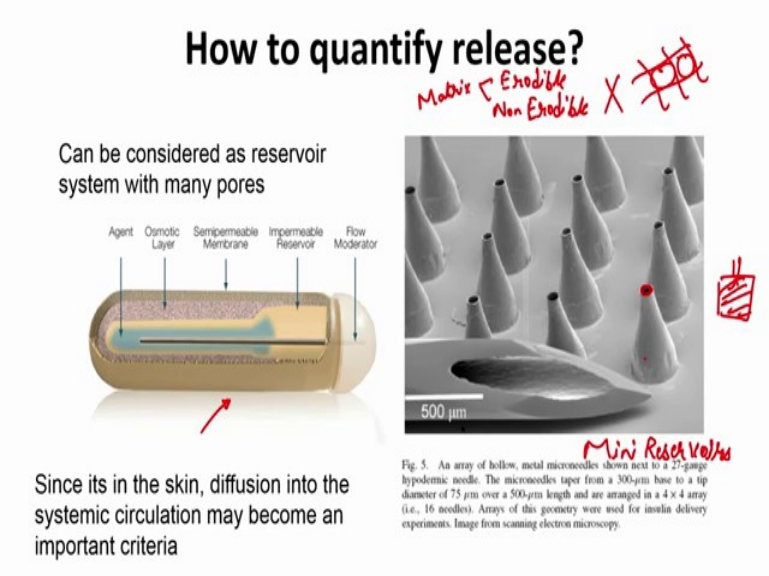

So, how will you quantify release from this? What kind of a system would this be? So, again if you look at this, what kind of system do you think it is? I will give you a moment to think about this. So, remember we have done several types of system right, we have done, we have done matrix based, in matrix base we have erodible, non-erodible or any of these that? You know it is not just because we know that in matrix system that drug is actually entrapped between the polymer chains this is not the case here. So, it cannot be this and what about a reservoir system?

So, in reservoir system we basically have some volume in which the drug is there and then there is some pore through which it can come out or some membrane, some osmotic driven pressure or osmotic pumps like things it can come out. So, this is actually what it is these are mini reservoirs, and so if you then can consider it with a very similar equation as we had initially talked about the reservoir system, in early earlier part of the course and since it is in the skin the diffusion into the system circulation may become also an important criteria. But essentially, at least for the drug to come out from these micro needles you can consider the same kinetics and equations as you did for these osmotic pumps base reservoir systems.

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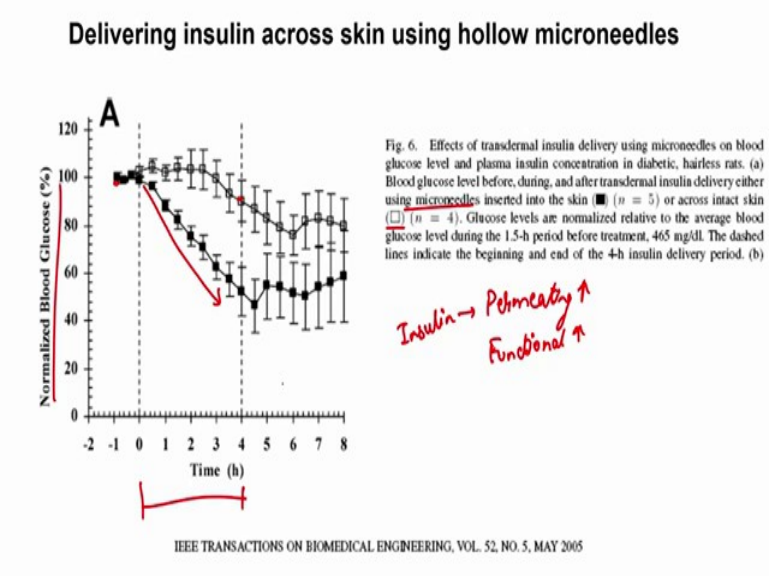

So, here is a more example here they are delivering insulin across the skin through some hollow micro needles. And so, what you see here is you have either, so in one case they have used these insulins or these insulin through the micro needles or in this open square they have only put the insulin on to the skin. And so what they are looking at is the level of the blood glucose in some animal and what they find is if you put it on the skin and this is a duration for which the treatment was given, you do not really see any change from the levels here to the levels here not any significant changes and then obviously, based on level changes is the mouse, so the animal itself is causing. But if you use the micro needles you see a stark drop in the level of the glucose.

So, not only, so this basically is showing is not only is the insulin permeating at a higher rate, it is also functional. So, we are not really causing any functional damage to the insulin because it is able to do its job in the body because we are measuring the blood glucose, so blood goes will only go down if insulin is functional and is able to act on its receptors.

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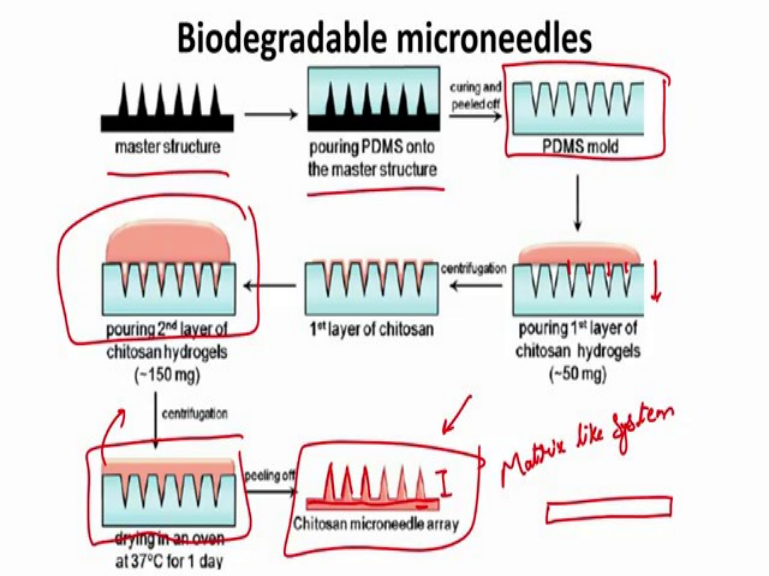

So, again because these sharps are also problem and you do not really want to use quite a lot of these titanium and metal-based things. So, you can also make biodegradable micro needles. And what it is? It is you have a master structure this could be of some metal or some other some other element. You pour PDMS which is one of the polymers that cures, because it is going to cure, it is going to cure and take the shape. So, you will essentially when you take this polymer off you get a mold like this and then you can come in with whatever polymer you want to make it out of, and just pour it over it give it some center position. So, that these cavities get filled.

So, you will get a system like this. You can pour another layer if you want to make multiple layers in that in that regards, and once you have done this you can cause the polymerization to happen either by heating or by some other trigger. And then you can again peel this off and what you have is micro needles of various kinds of polymer whether biodegradable, non-degradable, various properties in them and there are small structures.

So, even though you may you may think that these are polymer and they may not be structurally strong, but because they are such a small structure and they have a strong base for applications of micro needles they are actually fairly strong for them to penetrate the skin as well as not be able to kind of just break off or something like that for happening.

And then these could be water soluble or these could be water degradable, and what will what we mean is once you put it on your skin and it comes in contact with the water the skin is actually going to just cause in the degradation, and the drug to release and now this is going to become a matrix like system. And now you do not even have to worry about waste, right? I mean this is no longer sharps anymore because everything is going to degrade once you peel it off all you have is just a layer, a flat layer of polymer which is again degradable. So, you can you can just put it in water or you can discard it in a much safer manner then you will be the such a high number of needles that is currently being done.

So, needle ways discard is another big problem that is there in the field. So, this eliminates that. Especially in rural areas where there is not enough incineration of these tips or these needles happening it is a big problem. In fact, you may actually see quite a big piles of waste, and those wastes are actually very dangerous for people who work there because when they walk through them they can actually get these needles poked into their body and you never know what the needle was used for maybe it contains some pathogen and all. So, it is a bigger issue, ok. So, we will stop here, and we will continue rest in the next class.

Thank you.