Drug Delivery Principles and Engineering
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Lecture – 41
Route Specific Delivery Inhalation – II, Buccal and Rectal Administration

Hello everyone, welcome to another lecture for Drug Delivery Engineering Principles. We have been talking about Route Specific Delivery. It is essentially what route to choose for various applications. We have discussed several routes already and we have been now discussing inhalation. So, let us quickly recap what we did in the last class.

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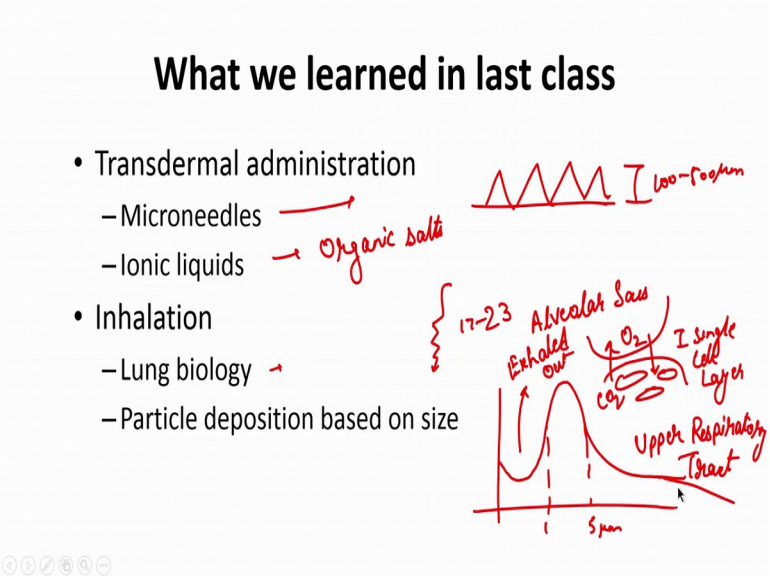

So, in the last class we finished our discussion on the transdermal administration, where we talked about microneedles, which are these small structures from 100 to 500 microns long. When they penetrate the skin, they only go deep enough to bypass the stratum corneum but, does not go and touch the nerves and the blood vessels, which is what will cause the pain. And they are actually very effective in terms of enhancing the permeation, that is one bioengineering approach.

The another is to use ionic liquids: these are organic salts that have high solubility for lipids and other kinds of molecules. They have been shown to enhance the permeation; basically you can classify them as a chemical enhancer. And so, they are able to enhance the permeability, but quite a high amount and we saw an example of insulin where if you

just apply insulin on the skin, it does not diffuse in, but if you apply it with these ionic liquids, it actually penetrates quite uniformly throughout the whole skin.

Then we started Inhalation, where first we discussed lung biology; we said that once you inhale things the air has to bifurcate several times, almost all the way to 17 to 23 times before it reaches the final compartment, which is nothing, but alveolar sacs. These are being surveyed by macrophages quite a lot and this is where the major absorption of the drugs happens and these alveolar sacs are actually very close to blood vessels. So, this layer is on just a single cell layer. And you have your blood cells floating around through this blood vessel. So, the absorption happens quite a lot at this place. This is where the gas exchange also happens. So, your oxygen goes in here and you CO_2 from the blood gets exchanged.

The lung is heavily vascularized, because all the oxygen that we get, happens by exchange at the lung itself. So, that is one and then we talked about how particle deposition on the basis of size happens in the lungs. So, what we found is especially for the deep lungs is, if we were looking for particle deposition. We are looking at the value which is something like this, where this range is about 1 to 5 microns. Anything below gets exhaled out and anything above gets deposited in the upper respiratory tract. So, that is what we had discussed in the last class, let us continue our discussion on inhalation in this class.

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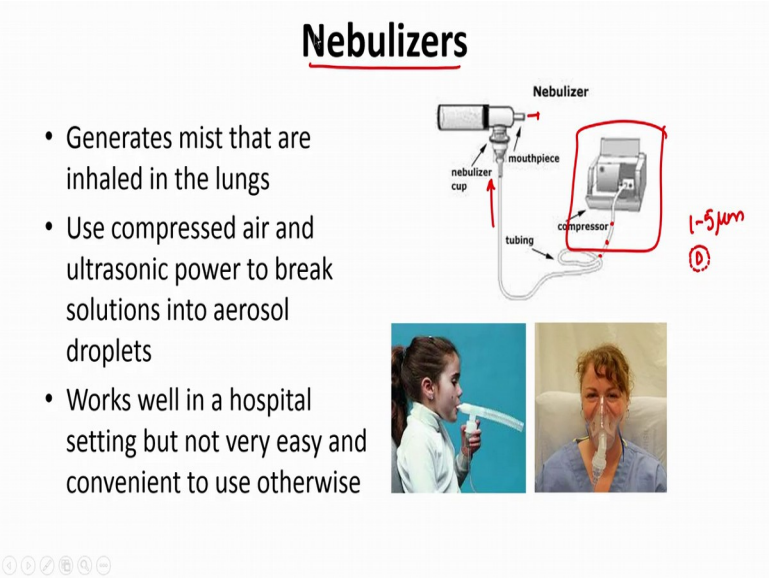

There are several types of inhalation; one is called nebulizer and you might have seen this in the hospital setting: this is nothing but a small nozzle that can go in the mouth. And then there is some kind of a compressor that generates small droplets. Your drug will be put in these tubing and these small droplets will be generated. What happens is, you have these small mists like water droplets that are carrying your drug and they are generated in the size range of word 1 to 5 microns.

So, when you inhale them, they go and end up depositing deep in the lungs where; obviously, this is just a water layer. So, that will just burst and your drug is then free to move around and get absorbed through the blood vessel. So, as I discussed, this generates mist, that are inhaled in the lungs and it uses compressed air and an ultrasonic power to break the solution.

So, the solution and the drug can be filled in here or here. And whatever is filled in, because of the pressure and the ultrasonic power generates mist or these aerosol droplets. This works very well in the hospital setting: it is a fairly complex instrument to use so, not something that one can use at their houses, but in the hospital setting it works very well, otherwise it is not very convenient to use.

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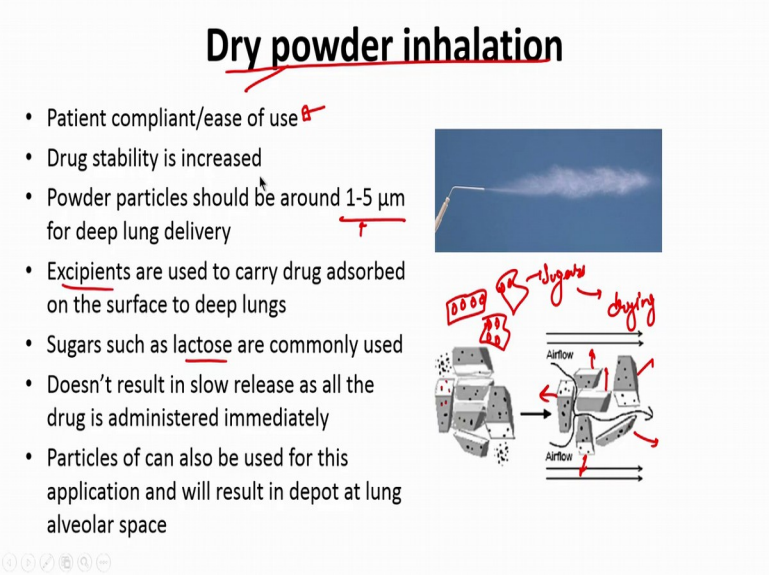

So, that is why if you were really want a patient compliance system, dry powder inhalation is one of the ways to go about it, because this is something that the patients can actually self-administer. For the previous case the patient will have to go to the

hospital. So, if you are looking for a therapy that requires nebulizer then it is not going to be patient compliant as the patient every time suffers from something or if it is a daily dose then they will have to go daily to the hospitals.

So, let us talk about dry powder inhalation which is extremely patient compliant and easy to use, again as in as I said multiple times. So, you might have seen patients with asthma using these dry powder inhalers and it is actually very well accepted by the patient. Since, it is in the dry format the drug stability is quite a lot improved. So, most of the reactions, most of the contamination, that may cause degradation, may be enzyme contamination, those will only work in aqueous environment. So, if you have a completely dry powder-based solution or powder-based drug, it is not going to be degradable to any of those components.

So, it is stability which is actually vastly enhanced. And then in this case if you are trying to deliver particles, then the powder particles should be at around 1 to 5 microns for deep lung delivery. Then typically some excipients are also added. So, that you can add your drug on to these excipients and the excipients are nothing, but small irregular shape particles, on which you can then adsorb your drug.

And these particles could be made out of sugars. And this have two purposes; one is they act as carrier for whatever free drug it is and they will deliver the drug to the deep lung. Because, if you only deliver the drug, which is very small, that drug is going to get exhaled out, it would not deposit. So, that is one advantage, other advantage is, it actually acts as a protectant at the process of drying.

So, when you are drying, you are doing some kind of either cryo or some other method and these sugars act as a very good product in for that. So, something like lactose is very commonly used; Mannitol is another one. And here is the example that I was giving you. So, these are these small sugar molecules and you can see that the drug is actually adsorbed on it.

And because these molecules are fairly large, they have actually a very large momentum and when the air flows the air is able to separate this out very well. So, all of them will get different velocities in different directions and that causes the separation. So, these particles then become very good in terms of delivering the drug to the deep lung.

However, this is not a control release, because whatever drug you are putting in is immediately available.

So, if the drug is extremely small, which most drugs are, let us say 1 nanometer, 2 nanometer these drugs is going to get immediately into the system. So, it was very well in terms of the delivery of the dry powder, but now if we talk about the control and sustained release which is the major part of this course, you do not really get that with this particular system.

So, this is where the materials come in so, maybe we can make particles which can then encapsulate these drugs. So, rather than releasing that drug immediately, we can have these particles have them in the right size range and then deliver them through inhalation. So, instead of using these sugars we may be using particle or maybe a mixture of particle and sugar. And then rely on these size ranges and aerodynamic properties to deposit deep in the lungs.

Once that deposited deep in the lungs, because we know that the mucus clearance is very low in deep lungs and they will act as a depot and then they can slowly degrade and release whatever they are carrying.

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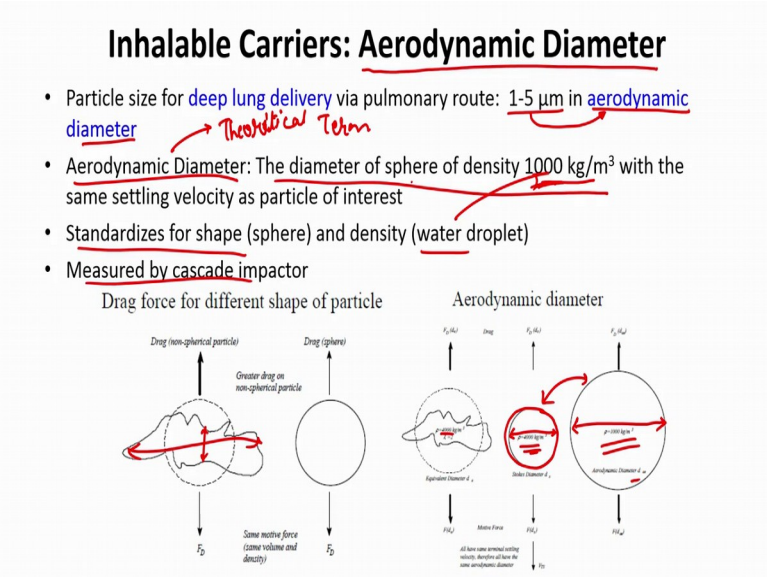

So, before I talk about particles and their properties, let us discuss one of the properties, which is aerodynamic diameter. So, this is nothing, but again the particle size range for

deep lung delivery by a pulmonary route we already discussed is 1 to 5 microns, but what I did not tell you earlier is these 1 to 5 microns, is defined as aerodynamic diameter range that it needs to be in. So, what is aerodynamic diameter? This is nothing, but this is the diameter of a sphere of a density 1000 kg per meter cube with same settling velocity, that a particle of interest.

So, this is a theoretical term. So, again if I have to define, this is theoretical term, it does not really have any physical meaning, but it is something which is defined which is a diameter of a sphere with this density. And so, if we are dealing with spheres, whether they are polymeric, those densities typically should lie at around 1000 to 1200.

So, that means that the physical diameter is actually equal to the aerodynamic diameter. However, if the particle density is different or if the particle is irregular shaped, then this is not the case and you will have to calculate the aerodynamic diameter for your particular particle. So, this is nothing, but to standardize the shape and the density. So, again the water is the same density as this, so, are the polymers.

So, this is measured by an instrument called cascade impactor which we will come to in a moment and essentially what it is doing is, it is taking into account various drag forces. So, if let us say you have a particle which is shaped like this, you will then have to assume it to be a sphere, which is somewhere in between the 2 axes of the particle.

And then you are basically measuring how much is the drag through your airway system and then equating it to this hypothetical sphere that you have drawn and that is how you can then and calculate the aerodynamic diameter. So, let us say a particle with a density of 4000 kg per meter cube, that is going to give you some diameter if you model it at 4000 kg per cube, but since it is the density is very high that drag is going to be lower for this.

So, to compensate for that you actually increase the size of this to say that and that aerodynamic diameter will be this diameter rather than this diameter, because now the density is different. So, the drag will be different. So, what you are saying is these two have the same drag, even though they have different densities in different diameters and that is what you are essentially comparing it to.

So, now, what we will learned is for the right size range you own the aerodynamic diameter to be 1 to 5 microns. And for whatever particle type you are using you will have to find a term to equate your physical parameters, the physical length breadth and the height of a particle to this aerodynamic diameter and density.

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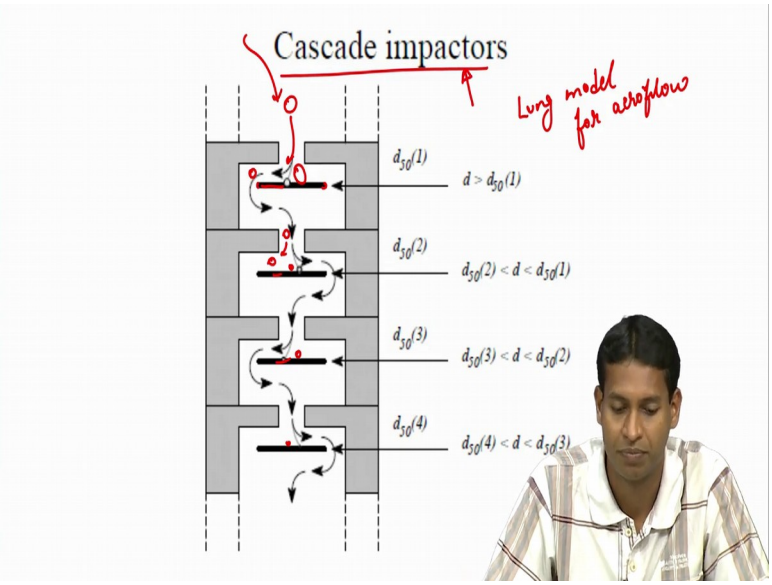

And I mentioned that cascade impactor is used to measure aerodynamic diameter. So, one is to you do all these theoretical calculations, but that requires you to know several parameters, which may or may not exist for a particular type of material that they are using in a particular shape. So, what you can do is, you can do it experimentally and this is called a cascade impactor. So, this is nothing, but it is a lung model, for air flow.

And what it contains? It contains a pump, that is pumping in air at a similar velocity that what we breathe in and it has several plates, which is actually acting as the bifurcation points in a bronchiole and several of them. So, and this plate is coated with some sticky substance. Whatever comes in contact with this plate gets stuck there. And it is so, designed that it actually models each and every of the bifurcation and stratifications of our airways.

So, now what you are modeling is, if something is coming and it is able to change it is direction with the air and continue to grow go, at some point it will start depositing. And depart depending on where it is depositing you can determine, what is the model aerodynamic diameter. So, you already have run some standards and you know which

plate will deposit a certain aerodynamic diameter and with your particular particles. You can then see which plate is recommending the most and get a distribution of your aerodynamic diameter in your vertical settings. So, again for most inhalation-based delivery this is something that is used to characterize your formulations.

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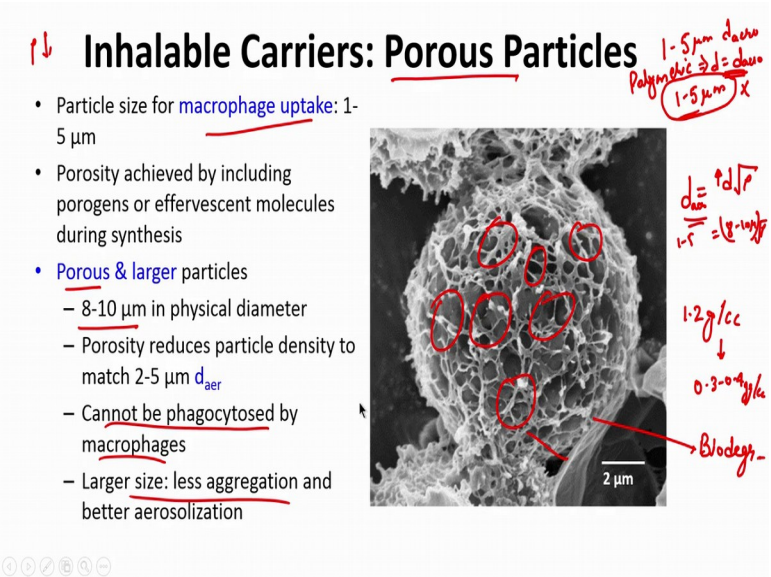

So, having learned all that I did not mention one thing that our alveolar sacs contain these macrophages, which are surveying these alveolar sacs and whatever is coming in, if they find anything foreign, they are going to clear it by up taking it. Now, that creates a problem. Because, we said to deposit deep in the lung, we need 1 to 5 microns.

However, we know that for at least for polymeric particles, which is what we have been discussing quite a bit in this course and for a spherical particle at least you have this d is equal to d arrow. So, now, what I am saying is for polymeric particles I will still be trying to make them at 1 to 5 microns. However, these macrophages that are there they have very high clearance of this size particle range, they are actually optimized to uptake particles in this size range.

So, now if I am delivering something which is in this size range and hoping it is going to make a depot it is actually not going to make a depot what will happen is these macrophages are going to take this up and clear it from my body. So, that is a problem right? because I do not want this for most of the drugs, if am trying to deliver it to the macrophages just well and good this is the perfect size, but if am trying to deliver it to go

to systemic circulation or trying to deliver it to go to epithelial cells, make a depot there and release things over time, that will not happen because these macrophages will clear them away.

So, to prevent that and this is again just seeing the same thing that the particle size for macrophage uptake is also 1 to 5 microns. So, to prevent that what we can do is we can change the porosity of these particles. Once, we change the porosity we are essentially changing that density. And now we are changing the density, we are now changing the drag. So, then what we are saying is this equation will no longer be true. In fact, this will change depending on the density if the density is going up or down your diameter will also change to be equal to the aerodynamic diameter.

So, that is what is done. So, what you can do is you can make them extremely porous; that means, that the density goes down which means that, if I write the equation for the aerodynamic diameter. I am talking about, if let us say everything else is and the same I am saying d is equal to the physical diameter, then daero is equal to d multiplied by square root of density.

So, now, if I have decreased the density to get the same aerodynamic diameter, I can actually increase the physical diameter or the actual diameter. So, that is what is done. So, if you make it extremely porous you can increase the size. So, as it is seen here this is extremely porous. So, now, it is mostly air and the polymer is much in lower amounts the density from let us say 1.2 gram per cc has gone down to about let us say 0.3 - 0.4 gram per cc, that has allowed me to change this 1 to 5 micron size range to let us say here 8 to 10 micron as there is multiplication with square root of the density. So, once I do that; that means, that now my particles are much bigger, 10-micron particles are just physically too big for these macrophages to be able to clear them away. So, now, I can still get that deeper.

So, what do you do, what is it written here is, it cannot be phagocytosed by the macrophages? And not only that, the larger the particle, the more the momentum is and because of that they tend to separate very well from the other particles. So, you actually have less aggregation when you try to aerosolize these particles.

So, this is required because let us say, in a dry format if 4 particles clumped together and do not separate out when they flow in the air, that will lead to quite a bit of a problem,

because now they are actually not in 1 to 5 micron they are in 4 to 20 micron range and that is not what you want. So, it is very important that, when you are aerosolizing these particles separate out. And so, larger the particle, the easier it is for it to separate.

So, these are the two advantages that it gives me and now I can use this particle and you can encapsulate my drug inside this is of course, biodegradable we can make it out of PLGA let us say. So, this is biodegradable and as it degrades, the drug will continue to release out and go into the systemic circulation.

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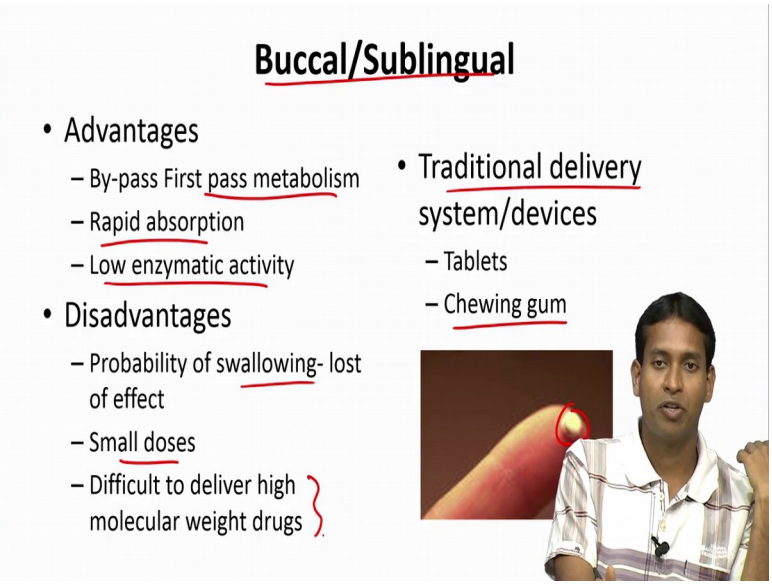

That is all, I had for the inhalation. Let us talk about another delivery format, which is Buccal or also called Sublingual. So, this is a very traditional delivery method, not used as much these days. And so, I doubt any of you might have actually used buccal delivery with any tablets, but what it is, you take a tablet and you just keep it under your tongue for a longer duration and that region is called the buccal cavity. So, anything below your tongue, cheek - all that region is buccal/sublingual cavity.

So, something like chewing gum is a classic example in which, basically all the taste is getting through the buccal cavity. And so, these are typically tiny tablets, because you cannot really keep a big tablet in your mouth and let it dissolve away completely in your mouth. So, it is not a good feeling to keep something in the mouth for long duration, that is why it has slowly and slowly moved away from use in the clinics. But still for some

tablets you will find that, it is recommended that the tablets be kept in the mouth for long duration. So, the advantage here are, this is actually avoiding bypass metabolism.

And we will come to how this actually happens, but this is not through the oral route. Even though you are taking it orally, the absorption into the circulation is happening through a different blood vessel, than what it does, when you take it through your stomach. So, that is different and it actually avoids first pass metabolism, there is a rapid absorption of the drug. And then of course, it is not going to quite a high concentration of enzymes which you find in the in your stomach.

Even though there are some enzymes in our mouth, those are in a much lower amount. So, your drug is a lot more protected when you are delivering through buccal cavity. Disadvantages, again as I mentioned already, first of all there is a probability of dissolving. So, maybe you would not be able to keep it for very long maybe it will you will just end up dissolving, as you can see here you can give very small doses. Because again you cannot have big things in your mouth floating around for quite a long time and the absorption again, it suffers from the sizing of the drug.

So, if you are trying to deliver a drug which is big it may not be able to permeate through your buccal mucosa.

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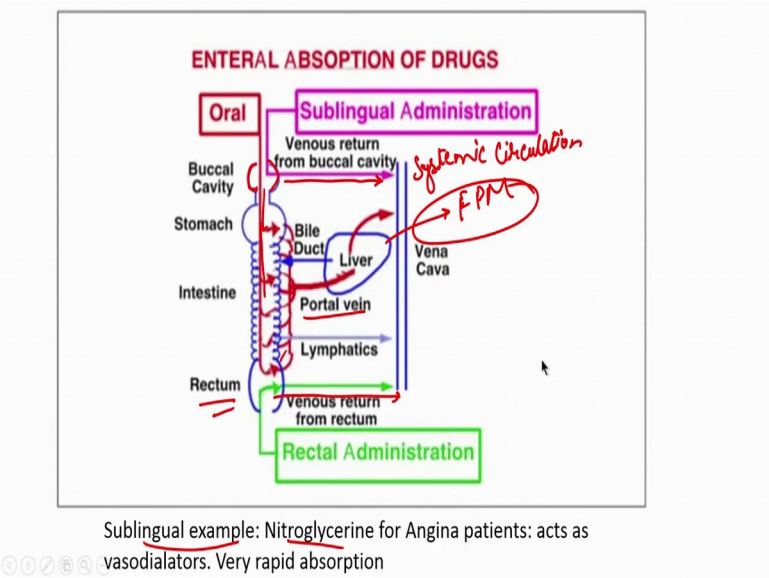

Sublingual example: Nitroglycerine for Angina patients: acts as vasodialators. Very rapid absorption

So, here is how it avoids the blood the first pass metabolism. So, if we are looking at oral route, we are saying that oral when you eat something. Obviously, there is buccal cavity, which I said it is right under the tongue or around cheeks, but you directly take the things to stomach. Once it is in the stomach, it goes to intestine and all of that goes to the portal vein to the liver where the first pass metabolism happens.

However, there is a separate vessel that is carrying molecules from the buccal cavity. So, here you have; here you have a separate vessel, that is sending it directly to the systemic circulation.

So, because of that you are now avoiding this first metabolism and the drug is much more protected. The same thing actually happens to rectum, in which, we will talk about next or maybe in the next few slides, where anything that is absorbed through the rectum area, that is a separate vessel and that is also bypassing the first pass metabolism. So, now, that the example of it is nitroglycerine is delivered to angina patients. It has very rapid absorption for at least this particular molecule it is a very small molecule and that is being delivered through this route.

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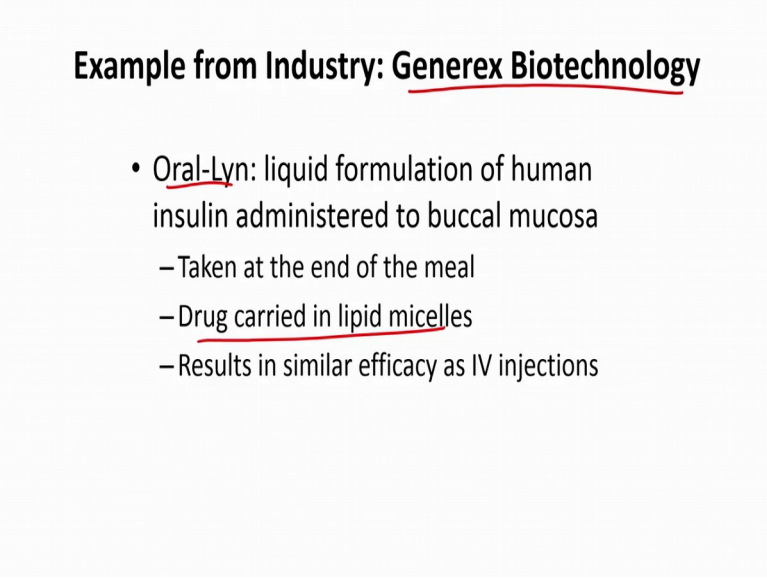

So, here are some more examples. Here, you have a product by generics biotechnology, which is called the Oral-Lyn. And this is nothing, but an insulin formulation which is taken at the end of the meal. And in this case the drug is actually carried in lipid

micelles, which are then asked to hold down in the mouth and gives a very similar efficacy as IV injections.

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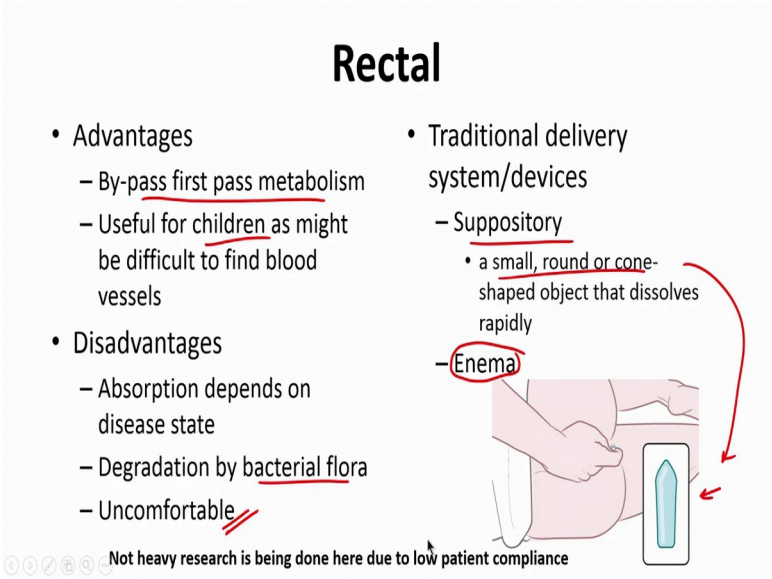

Let us talk about rectal delivery now. So, rectal delivery as the name suggests is basically delivery through the rectum. And this is again not very widely used anymore, it is a very traditional form of delivery. So, something like this device is inserted into your rectum. So, here the drug is nothing, but a small round cone shaped object, which is this and sometimes enema also used which is a liquid formulation which is poured into your rectum as well.

So, the advantages as I briefly mentioned in the previous slide, it bypasses the first pass metabolism because there is a different vein that takes it to the systemic circulation. And it is actually very useful for small children's and babies, because it is actually very hard to find a blood vessel for them. And obviously, they are not going to be compliant enough to hold their drugs into their mouths.

So, in buccal cavity, blood vessels are hard to find, they have a very small muscle at that point of time. So, you cannot really use that area the only other remains in the subcutaneous, but I mean with children is actually very difficult for them to agree with injections. So, that is one of the ways that people can do this and it is also something that parents can easily do this. So, parents may not be comfortable handling needles injecting

their babies they might be afraid that maybe the needle will hit a blood vessel which is not what they want.

But this is something that the parents can easily do and so, it is very widely used for children only. Again, there is several disadvantages, first the absorption depends on the disease state. So, and there is degradation by bacterial flora. So, all of these rectums are filled with lots of bacteria. So, these bacteria can actually degrade some of these drugs.

And of course, it is extremely patient non-compliant as it is very uncomfortable. So, not a whole lot of delivery is going to happen through this route. And again, because the same reason even the research is not being done quite a lot through this route anymore.

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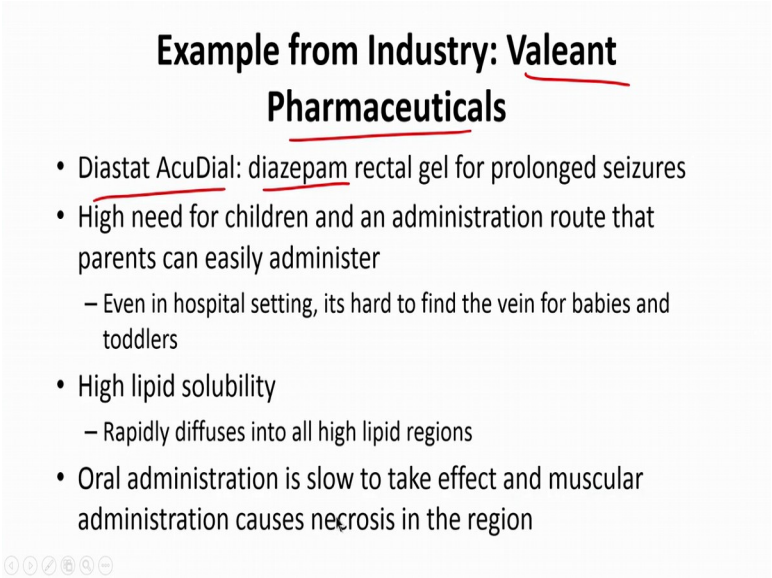

So, here is an example from Valeant Pharmaceuticals. So, this is called the Diastat AcuDial and it is a rectum gel that diazepam is delivered through this is, to prevent seizures. So, if somebody suffering from seizures then this can be given so, again a caretaker can give this. So, if the patient is of course, incapacitated. So, it cannot eat anything it cannot put it in the buccal cavity, if the attendant is not very well trained; maybe it is the father mother or the child, they do not really know how to do the injections, they may not have access to injections and then they can just take the suppository and put it in the rectum.

As I said this is a high need for children, parents can easily administer it even in the hospital setting, it is hard to find vein for babies and toddlers and this has high lipid solubility.

So, it rapidly diffuses into all high lipid regions and this particular drug the diastat acudial diazepam. And the older administration is slow to take effect and then again in the babies especially you do not want to punch the muscles too much, because it can cause necrosis and prevent development from happening.

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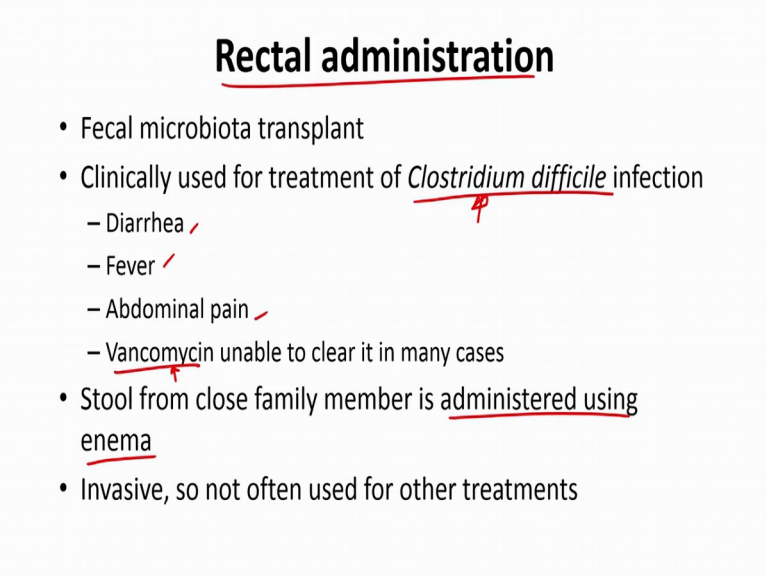

So, here is another example of rectum administration, it is called the fecal microbiota transplant. So, this is one of the things that is actually very widely used even now, well not really very widely used, but at least it is coming up in a quite enthusiastic fashion and some research is actually going on this. And so, what it is, this is clinically used for an infection, which is Clostridium difficile. It causes severe diarrhea, fever and abdominal pain and the drug or the antibiotic is not able to clear it in many cases.

So, you can continue to take this drug, but lots of time this Clostridium is actually very persistent and you are not able to clear it. So, at that point what is done, is stool from a close family member and family member there is a similar eating habits like the patient, is then administered through enema. So, their stool is taken and it is converted into a liquid slurry and then this is administered through the rectum route. It is fairly invasive.

So, it is not really used for any other treatment, but with this particular case it is seen that it is actually very effective, much higher efficacy than delivering these vancomycin-based drugs. And the patient can then stop suffering from diarrhea and fever and this therapy is now actually used quite a lot in clinics. Okay! We will stop right here and we will continue the rest in the next class.

Thank you.