Drug Delivery Principles and Engineering
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Lecture – 40
Route Specific Delivery Transdermal and Inhalation Route

Hello everyone. Welcome to another lecture for Drug Delivery Engineering and Principles. We are on the module where we are discussing different routes of administration. We have discussed quite a lot in this course already and at this point let us quickly recap what we learned in the last class and we are going to continue our discussion on different routes of administration as we go along in this class as well ok.

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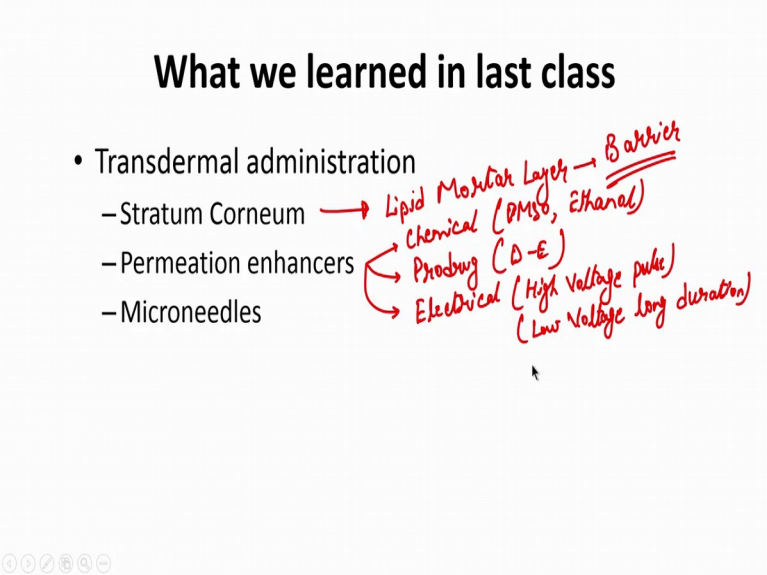

So, we looked at transdermal administration in a little more detail. So, remember we are saying that stratum corneum is a major lipid mortar layer, that is responsible for causing a very tight skin barrier and this is the major challenge when you are looking to deliver things trans-dermally.

Because most of the drugs is not able to penetrate through this barrier. Then we talked about some of the strategies to overcome this barrier and enhance the delivery. So, one was permeation enhancers. In this we discussed several cases; we talked about chemical enhancers, using things like DMSO, ethanol etcetera. We talked about product approach.

So, rather than mixing them together we can actually conjugate them together and you can have D enhancers conjugated together. We talked about actually physical damages. So, this could be electrical waste, so high voltage, high voltage pulse or could be low voltage, long duration and then apart on that we also discussed several other methods such as laser-based damage to the stratum corneum, ultrasound-based damage to the stratum corneum.

But with all that all of this there is a risk that we may expose the skin to several pathogens it should be done in sterile environment and should be very transient and there is always some risk involved in these cases. We also talked about bombardment as well when we talked about permeation. And then towards the end we discussed microneedles: it is one of the approaches where you make these needles in a very small dimension.

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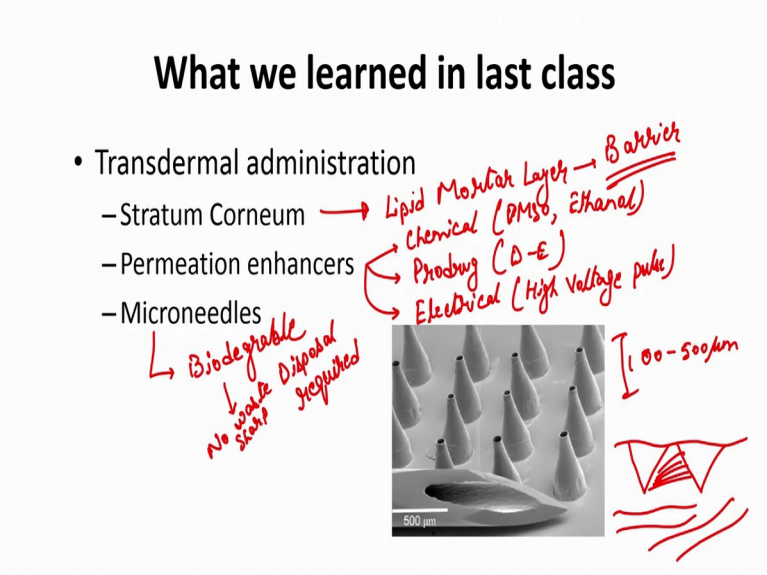

So, anywhere between 100 to 500 microns and what is seen when you make these needles of this size range, is you if let us say, this is the skin surface you are able to penetrate through the skin, through this barrier of lipid and mortar layer and but you are still further above, the blood vessels and the nerves.

So, in that way you can bypass the barrier increase the permeability, but quite high amount because this is what was causing, decrease in the permeability but still not be able to cause pain. And then we also talked about making biodegradable micro needles. So, we talked about making this biodegradable and what that gives an advantage is first

of all we can use all kinds of polymers and all kinds of materials rather than being limited to metals and then secondly, there is no problems of no sharp waste disposal required. And that helps quite a lot in terms of decreasing the cost of these sharp waste disposal and is very environmentally compliant.

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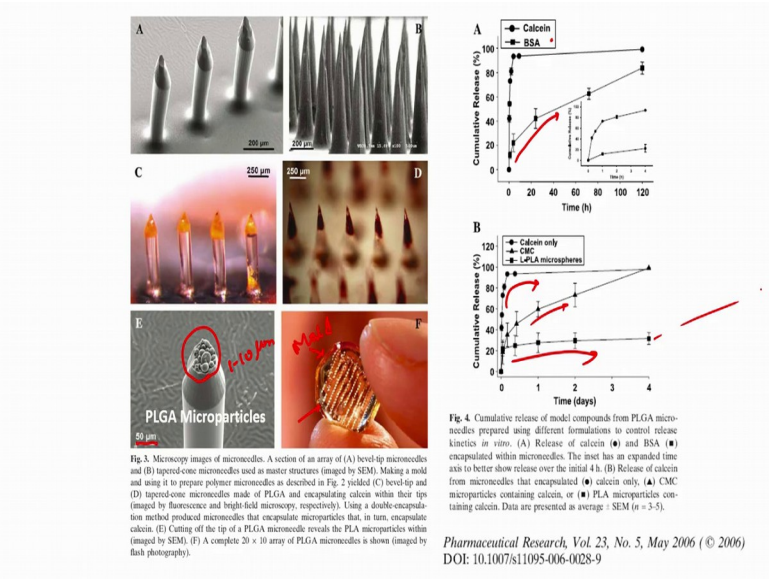

Fig. 3. Microscopy images of microneedles. A section of an array of (A) bevel-tip microneedles and (B) tapered-cone microneedles used as master structures (imaged by SEM). Making a mold and using it to prepare polymer microneedles as described in Fig. 2 yielded (C) bevel-tip and (D) tapered-cone microneedles made of PLGA and encapsulating calcein within their tips (imaged by fluorescence and bright-field microscopy, respectively). Using a double-encapsulation method produced microneedles that encapsulate microparticles that, in turn, encapsulate calcein. (E) Cutting off the tip of a PLGA microneedle reveals the PLA microparticles within (imaged by SEM). (F) A complete 20 × 10 array of PLGA microneedles is shown (imaged by flash photography).

Fig. 4. Cumulative release of model compounds from PLGA microneedles prepared using different formulations to control release kinetics *in vitro*. (A) Release of calcein (●) and BSA (■) encapsulated within microneedles. The inset has an expanded time axis to better show release over the initial 4 h. (B) Release of calcein from microneedles that encapsulated (●) calcein only, (▲) CMC microparticles containing calcein, or (■) PLA microparticles containing calcein. Data are presented as average ± SEM ($n = 3$–5).

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So, let us continue further with a microneedle. we are going to go into much more financial systems in the microneedles in this class and so, there as here are some of the examples. So, they have taken Calcein and BSA which typically have low permeability, through the skin and what you are seeing is here are various examples of micro needles first of all in terms of the Calcein and BSA also.

We see that quite a bit of the Calcein is getting released immediately into the system almost 100 percent and BSA being a larger molecule has a much slower release from the drug, whereas you can use other kinds of polymers as well. So, if we look here what we see is micro (Refer Time: 05:20) knows a different dimension, this is how by the way the chip will actually look like. So, you have some kind of a mold and very tiny micro needles this is to the scale if you can see this is a finger human finger.

So, this is actually zoomed in a bit and what you what you will find is these microneedles is so, tiny that you cannot even see them even if you poke through them you cannot even feel them because they do not touch the nerves and you can have these hollow micro needles and you can even deliver PLGA micro particles of fairly big size

or even if you look at the scale bar here, you are talking about 1 to 10 micron size particles can also be delivered and they can act as a deeper under your skin as well. So, just some examples of how these micro needles are being used. So, if let us say the drug is coming out so, quickly you can then encapsulate that into micro spheres which has been done here. So, you can see the free drug was coming out very rapidly.

So, what they did is they started adding some polymers to it or they encapsulated into microparticles and now you can have release happening over a period of quite a long duration.

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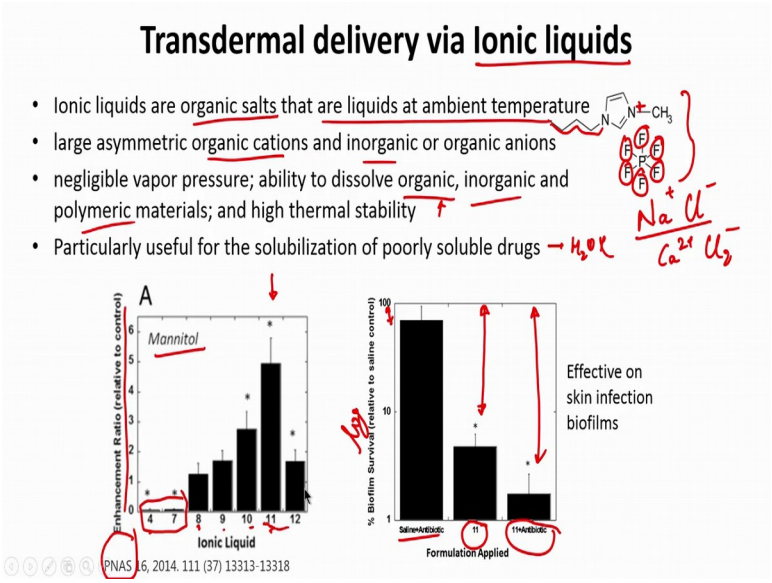

So, let us take an example of another research paper which was published in 2014 and they came out with another system which they called ionic liquids.

So, what are ionic liquids? Here is an example of an ionic liquid. Ionic liquid is nothing, but that as the name suggests they are ionic, but in this case, they are organic salts. So, when we talk about traditional ions we are looking at let us say salts like NaCl and when these salts are in the aqueous phase they are nothing, but Na positive and Cl minus and they are just floating around and interacting with other Cl and other Na ions as they move around, but in cases of ionic liquids we are talking about organic salts.

So, as you can see this is an organic molecule, carbon based and this in general has a positive charge, because of the presence of these amines and then these corresponding

negative charge is being provided by these fluoride based compounds and so, very similar to what we have in cases of our normal salt, these also when you put them in a solution they are also floating around; however, they are organic in this case. So, they are quite amphiphilic in fact, they are quite lipid liking ions that are there. So essentially, they are liquid at room temperature. These are again large asymmetric organic cations and when I say asymmetric, you can see here the charge is equal although you can have charges which are not equal as well.

So, if I have calcium chloride, you are talking about something of this configuration, but in this case, there is a large asymmetry in the organic cations and the inorganic or so, there could be organic cations, there could be inorganic cations and vice versa for the anions as well, but it has to be at least, one part should be organic and they have negligible vapor pressure. So, they do not really evaporate, but they have a very high ability to dissolve organic, inorganic and polymeric materials, plus they are actually very stable at high temperatures. I mean most of these salts they are not really very stable at high temperature, but some of these organic salts are actually very stable at high temperature and not only that they can actually dissolve organic, inorganic and polymeric materials, which is what you will find in the skin layer. Right? I mean we have talked about having a high lipid molder layer and then we have cell cytoplasm and some fluid around as well. So, all of that is something that these ionic liquids can handle. They are actually very useful in solubilization of some poorly soluble drugs in water.

So, if there are some drugs that are not getting solubilized in water, these ionic liquids, can be used to solubilize them. So, if they are extremely lipophilic or they have some property that causes the insolubility in water, you can use these ionic liquids to dissolve them. So, now, what is done here? So, these authors then went ahead and tested these ionic liquids for their enhancement ratio for a molecule called mannitol which is nothing, but a sugar.

So, they have tested various different kinds of ionic liquids. So, these numbers just suggest different kinds that they had and then they looked at how much they are enhancing with respect to control. So, some of them like ionic liquids 4 and 7 identity enhance any transport of mannitol from the skin surface to the inner part of the skin, but some of the others such as, look at this 11 quite a lot of enhancement, almost 5 to 6 fold enhancement, in the permeation of this mannitol. And again, the concept here is same

that these ionic liquids are extremely good solvents and they can disrupt this lipid mortar layer and cause the enhancement to happen.

And then they looked at a skin biofilm, which is actually very difficult to treat because as we have discussed in the previous classes the antibiotics are not able to kill the bacteria in the biofilms. The amount of antibiotic that you actually need to kill a bacteria in a biofilm is almost 1000 fold higher and then what it is for bacteria which is not in the biofilm.

So, here you can see, here if you treat the biofilm with just antibiotic and saline you find that there is almost no reduction. So, it is almost 100 percent surviving whereas, if you treat just with the ionic liquids itself, they are actually acting as such a good solvent and such a good disrupter of these biofilms, that almost more than an order of magnitude has got disrupted. And now if you add antibiotic with these ionic liquids, there is further enhancement of the efficacy.

Remember this is on the log scale so, it is quite a bit reduction that you are looking at with these ionic liquids. So, one application is here.

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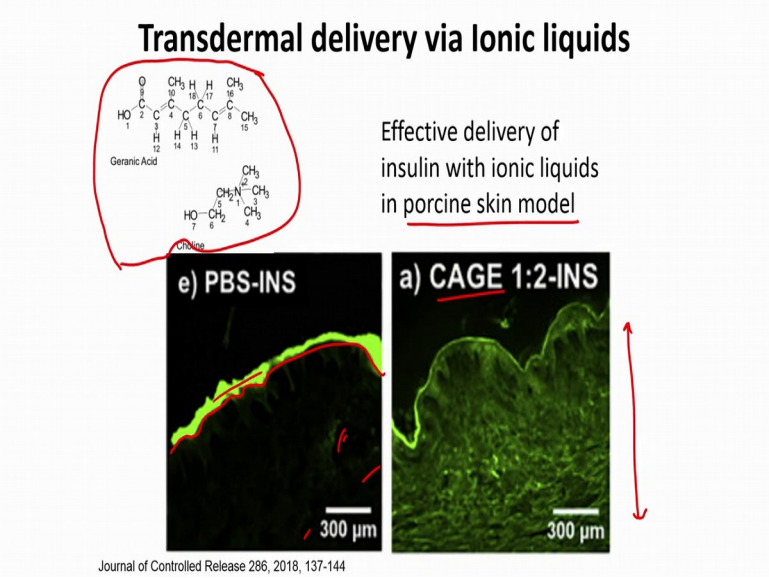

And then they have looked at whether these ionic liquids can actually transport drugs across the skin layer. So, what they are looking here is they have porcine skin model. So,

they have collected pig skin which is quite thick similar to humans. So, this is the skin surface, of this porcine skin.

So, what they first done is they have labeled insulin, which is which is a molecule required for treatment of diabetes and they have put it on the skin and looked at it after some time. So, what they find is if they are just putting insulin, what you can appreciate from this figure is all nearly 90, 95 percent of it is on the skin very little amount is actually going and penetrating inside the skin.

However, if they use their cage which was one of the molecules, again the ionic liquid, the geranic acid and choline ionic liquid and if they use this 1 is to 2 with the insulin, then you can see you can appreciate how much the permeation is increased. is actually very uniformly distributed throughout the skin and it will continue to permeate inside. So, you can actually deliver quite a lot of your insulin through this method ok.

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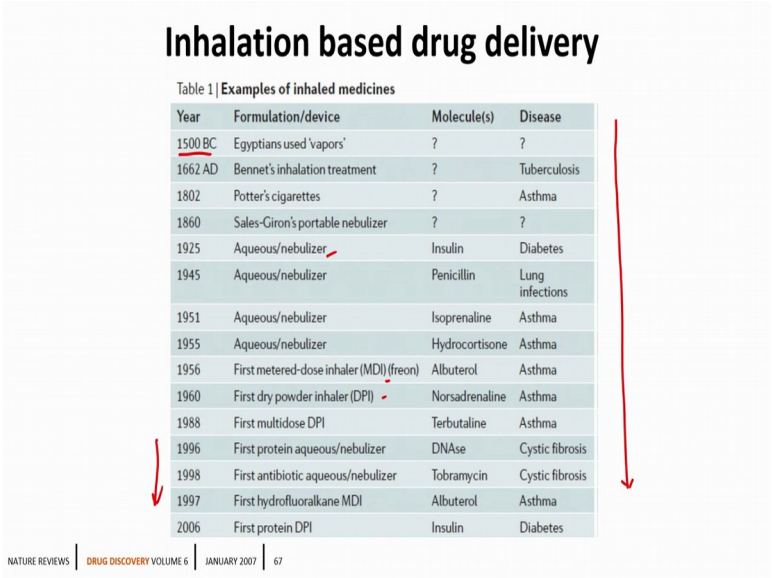

So, we will stop there for the skin-based methods we will now switch gear and we are going to go for inhalation-based drug delivery. So, inhalation based drug delivery is not new, again it has been used for quite a bit of time in fact, all the way back to 15000 BC where some of the Egyptians were using vapors to deliver drugs and obviously, this progress has increased in the last few years as you can see not much development, but towards the last you can start to see quite a lot of products starting to come out in the market and we will discuss some of these nebulizers and MDI and DPI as we go along in

this class, but that is just this is just to point out that it is actually being used quite a lot in humans.

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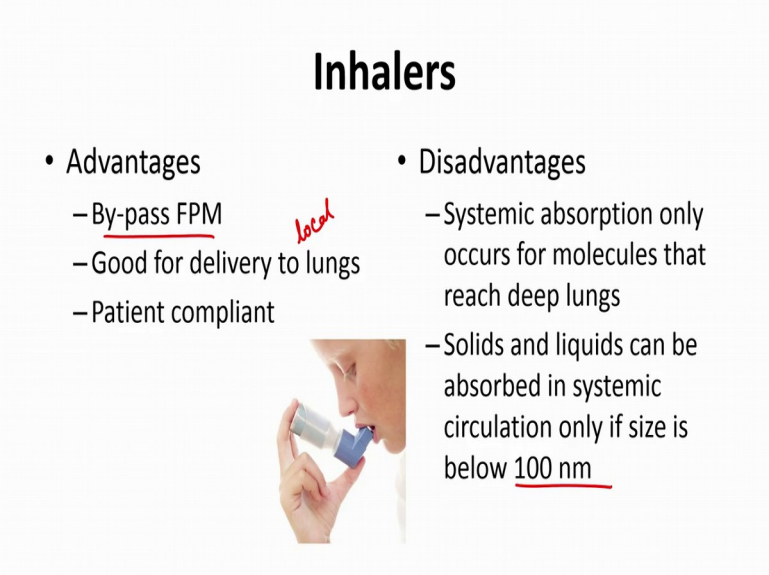

And so, what are some advantages of using inhalation? So, first is of course, it bypasses the first pass metabolism. So, anything which is not oral or not through your intestine is going to bypass your first pass metabolism, it is extremely good for local delivery to lungs. So, if you want local delivery and to lungs only, this is one of the best ways out there because everything you take in it is first going to go to the lungs and then if it is small enough it can distribute out to the rest of the body.

So, if let us say you are trying to treat lung cancer or you have asthma or some lung disease that you are looking at cystic fibrosis this is maybe inhalation maybe the best route to go about it rather than delivering the drug to all over the body and then the amount of the drug that bridges the lung is much lower and then you may have some associated toxicity in the rest of the body regions and it is fairly patient compliant you may have seen people using inhalers for asthma and so, it is just fairly easy to use rectally accepted very well there is no risk of injuring the person, which might be the present in cases of needles. So, these are some of the advantages here. However, there are few disadvantages the systemic absorption of these molecules can only occur once the drug actually reaches deep lungs.

So, if I just inhale something and if it is just localizing in the upper respiratory tract, in my nose, in my upper lung like trachea and all, these drugs are not going to go to the systemic absorption they will be removed by the lung itself and obviously, the solids and liquids will only be absorbed into the system if it is below 100 nanometer. Anything which is greater than 100 nanometer it is going to localize to lung we won't be able to pass through the lung and again we will discuss some of these as to why this in next upcoming slides. But these are some of the disadvantages, when you are looking at inhalers. Okay!

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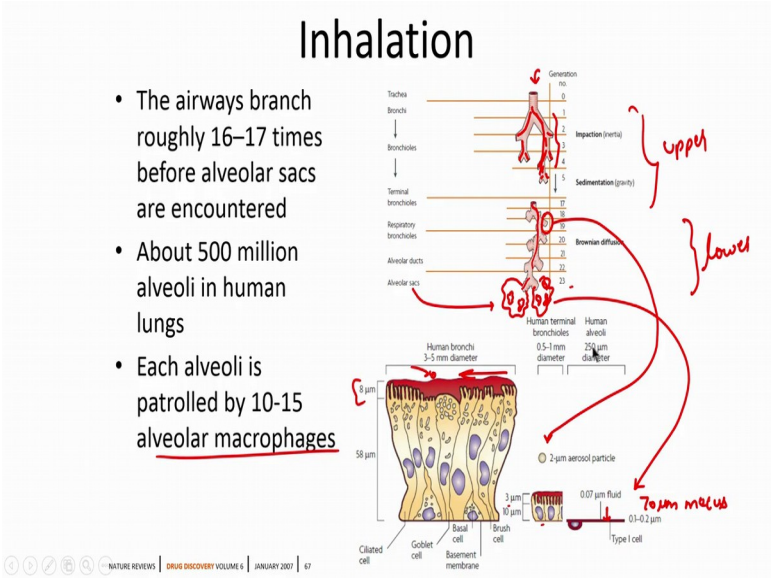

So, let us look at our lung route. So, our airways which are nothing, but several small branches which carry the air all throughout our lungs; roughly branch about 16 to 17 times, before they reach alveolar sacs and what are alveolar sacs I will come in a moment.

So, as you can see these are the airways. So, this is trachea, which is in your neck region and they actually continue to divide several times. So, you can you can appreciate. So, this is first division, this is second division, this is the third division, this is a fourth division this is fifth division. So, this is going to continue to happen about all the way up to 17 to 23 times, before it actually reaches the final alveolar sac. So, let us say this is the alveolar sac which is in the deepest part of our lung. So, and that is where you want most of the time when you are trying to do inhalation that is why you are trying to deliver

things. So, I mean it is a very intricate network in our body we have got about 500 million of these structures per human lung and so, it is a quite a lot of surface area and that is where the major lung function and then the major lung and dynamics is happening and so, this is the area that you essentially want to target.

If you are trying to deliver something through inhalation problem and then what further complexes is; obviously, the body has evolved over quite a few years and it has put in a lot of surveillance in this area. So, all of these alveolar sacs, they carry macrophages or immune cells, about 10 to 15 macrophages per sac. So, quite a lot of surveillance that is going around so, these immune cells are ready to take up anything that you are trying to deliver which these macrophages may identify is something for in and clear it away.

So, that is another challenge most of the time when you deliver drugs you do not want to deliver to these alveolar macrophages, you want to deliver to maybe epithelial cells , maybe let it go to systemic circulation and these macrophages impede those processes and one other challenge here is the mucous layer. So, we all know that our lung is lined with mucous and so, here is an example.

So, if you are in the upper region of the lung and this is how it would typically look like, you will have a thick mucus layer about 8 micron, you have these long goblet cells that secrete this mucus and if anything gets stuck to these mucus layer, that will not be able to move further and, but as you go further down. So, as you go down to smaller and smaller vessels. So, let us say somewhere down here, you have a scenario where these goblet cells are smaller as well as the mucus layer is also small.

So, it is 3 micron and then finally, when you go to the alveolar sacs, we are talking about a very thin layer of cells, with a very thin layer almost about 70 nanometer, very fluidic layer of mucus. So, if you want to deliver things, what happens is now our lung apart from these immune cells, our lung also has a system in which this mucus layer continues to go up, through these lungs and get eliminated. And this transport of this mucus is much higher in the upper regions, then in the lower regions.

So, if let us say you deliver something and it gets stuck in the upper region, due to this mucociliary clearance that is going to take this mucus away and along with that anything that is stuck to it all of this will get eliminated from the lung and we will actually either just go down back to the stomach or will get eliminated in some other fashion.

So, that is what you want to avoid. So, the ideal way is to deliver it here, here the transport of this mucus is very little this because the thickness is so, low and the residence time of the drug that you are delivering here is much higher. So, it will have more chance to act on whatever it wants to act on as well as get systemically absorbed and we will come to how some of these processes happen.

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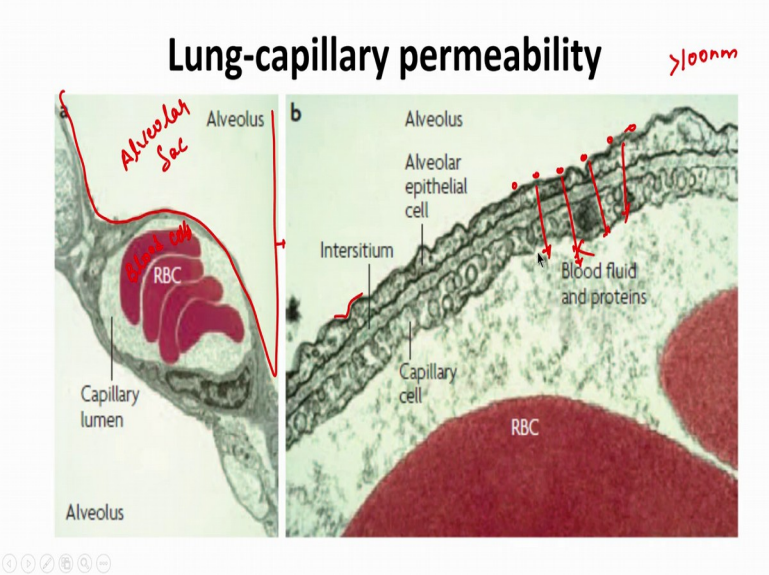

So, this is basically. So, if I go back again, if I zoom in as to what happens at this interface this is what it is. So, here is an SEM image which is false colored and what you are seeing, is you have this is your alveolar sac. So, all of this is, alveolar sac zoomed in and right next while we were saying you can see that there is a blood vessel going through which has blood cells, flowing through it and this is then further zoomed in here.

So, again this is your alveolar sac, here is your cell layer with a very small thin layer of mucus here and your blood vessel is right here. So, if you are able to deposit your drug onto this surface, it is easy for this drug to then diffuse and go into the blood and once it goes into the blood it is in the circulation. So, it can then travel very easily throughout your body. So, that is what you are trying to achieve and that is the reason that we said earlier that if your particles are greater than or if the drug is greater than 100 nanometers, then this diffusion is going to be stopped, because these are too big to be able to diffuse through this layer, but anything below 100 nanometers it just rapidly goes through here

and it is going to get absorbed into the systemic circulation. So, here is some of the lung biology and that we need for designing some efficient delivery system.

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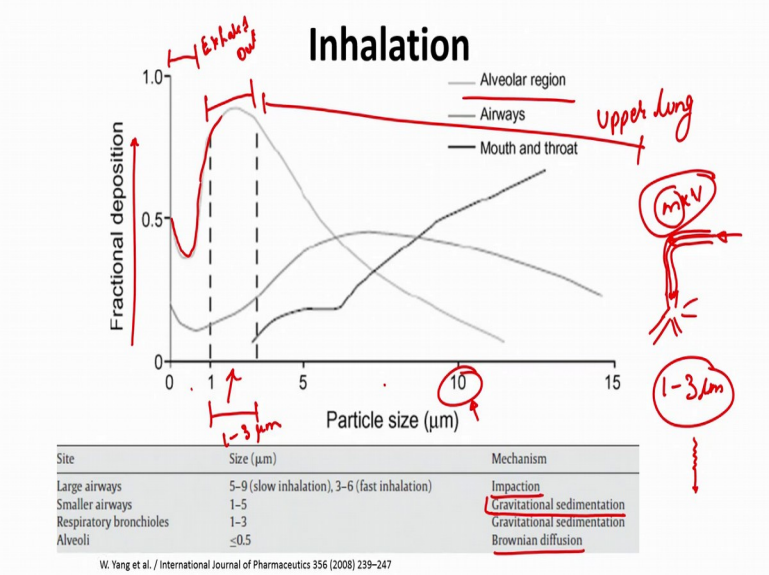

Site	Size (μm)	Mechanism
Large airways	5–9 (slow inhalation), 3–6 (fast inhalation)	Impaction
Smaller airways	1–5	Gravitational sedimentation
Respiratory bronchioles	1–3	Gravitational sedimentation
Alveoli	≤0.5	Brownian diffusion

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So, now let us look at inhalation and what are the properties here. So, for free drug again it is fine that we somehow need to deposit it in deep lung and once it gets deposited, it is going be able to go in systemically absorb. What about the particles in general what about the materials that you want to deliver? So, here is a deposition pattern. So, this shows fractional deposition as to how much fraction deposits in the deep lung. So, this is or in various regions basically. So, this is the alveolar region, which is this guy and this is what we are most concerned with, although we can model for others as well and what we find is the fractional deposition is very high, in the size range of about 1 to 3 microns.

So, if you have a drug or if you have a particle which is sized 1 to 3 micron and if you inhale it, then the chances of this depositing in this layer, in the deep layer is much higher and thereby the chances of it getting systemically absorbed and being efficient in whatever it is trying to do. Because if you make it too low then the these size ranges are actually exhaled out whereas, these size ranges as you can see from these graphs get deposited in the upper lung, and why that is the case? That is the case because basically there is an interplay of 3 major mechanism, which is the gravity, gravitational sedimentation, the impaction and the Brownian diffusion and what does all of these means? So, let us say this is what your trachea is and then it starts splitting into several

small capillaries and so, what happens is when you inhale things and if the, particles of the drug are large molecule let us say 10 microns then they have a very high momentum right?

So, the momentum is mass multiplied velocity and they have a very high momentum because their mass is fairly high and so, what will happen is this is called impaction, where they will just impact and rather than moving along with the airflow they just have too much momentum and it is very difficult in the mass in the momentum conservation.

They will not be able to change the about that quickly and they will just hit the back wall or some wall here at the time of bifurcation and trifurcations and once they hit the wall, they will get stuck to the mucus. So, that is why the bigger particles get accumulated right in their upper airways, what about the smaller particles let us say my particle is 100 nanometers.

Now, these particles are so, tiny compared to 10 microns. So, 10 microns is almost 100 times in diameter and since 100 times in diameter, the volume is actually even higher as it is directly proportional to cube of R. So, we are talking about 10 to the power 6 times heavier. So, if you have 100 nanometers particles, they are extremely light. So, their momentum is actually very low and they can flow with the streamlines.

So, what happens is these particles will tend to go with the stream line all the way down to alveolar sacs and then with the air flow itself they will come out. So, the air flow; obviously, decreases as it goes down and then it further increases when it comes back. So, as we inhale and exhale. So, that is why you do not see a much high deposition of very small particles in the lung whereas, if you are between 1 to 3 microns, at that size range what is been found is the momentum is not that high to impact the upper airways.

So, they continue to flow, but once they reach the deep lung because there is still heavier than your 100 nm particles, the gravity takes over and the Brownian motion takes over and they start moving and with the gravity start to fall as well. So, at that size range is found that they have at enough momentum and enough gravitation that an alveolar sac where the air velocity is fairly low, they can deposit and that is why the deposition in the deep lung is very high, compared to any bigger size or a smaller size particle. So, that is the major concept behind all this inhalation-based delivery. Ok! we will stop here and we will discuss rest in the next class.

Thank you.