Drug Delivery Principles and Engineering
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Lecture - 35
Route Specific Delivery Oral Route – I

Hello everyone. Welcome to another lecture for Drug Delivery Engineering and Principles. We have been talking about various kinds of strategies to improve drug delivery. For the past few classes, we went into tissue engineering module where we are talking about scaffolds which will stay in the body for quite a bit of time. While we were doing that there were some issues and challenges that had come up, which is one of the major challenges was the implant associated infections.

So, for the last two classes, we discussed how these implantation infections can be problematic.

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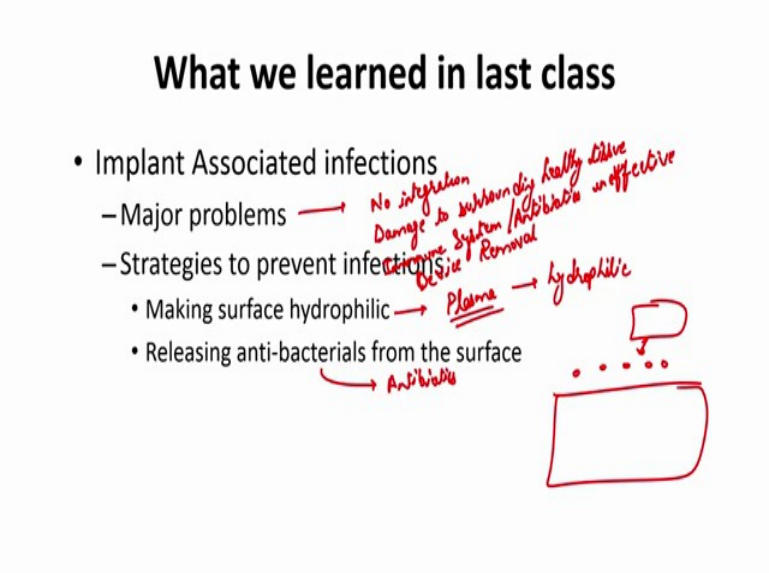

So, we talked about some of the major problems. That the tissue would not integrate, so no integration. Once they are infected, we also talked about that they will even cause damage to the surrounding. And then we talked about that there is really not much you can do because those implants are sort of resistant to the immune system as well as antibiotics and really the only option that comes after that is to remove the device. So, whatever you have put in you have to remove it; make sure that the area is no longer

containing any bacteria and then you put another device or you take cognizance of what needs to be done in the patient.

So, some of these strategies we also discussed to prevent this from happening. Of course, this is a road we do not really want to go down to. So, if we can do it in such a way that it does not happen that will be great. So, in that we discussed some of the alternatives that we have; so, let us say for a particular application we have multiple alternatives in terms of polymers, in the type of material we are using.

So, we can then go ahead and maybe use the ones that have been shown to be less prone to infection than the ones that have been shown to be more prone to infection. Of course, you have to make sure that the device itself is actually useful, if you want to grow a liver, you do not want to put a stainless steel implant there just because it may be less infective than let us say a polymeric implant, just because the stainless steel is not going to do anything in terms of repairing the tissue. So, some of these things again you have to take into account.

And some other strategy you discuss is to make surfaces hydrophilic. So, you can treat surface with plasma or some other options you can explore to essentially make them hydrophilic and what we typically find is bacteria adherence on the hydrophilic surface is low.

And another strategy we discussed was to release some antibacterial from the surface. So, this could be antibiotics or some other small molecules. And if your implant is already releasing these antibiotics out in the surrounding media then these bacteria are not able to come and attach to the surface because this will kill the bacteria or the bacteria will just go away. So, these are some of the things we discussed in the last class. We are going to now move on to a different module in this course and that is essentially what route you want to take for different applications.

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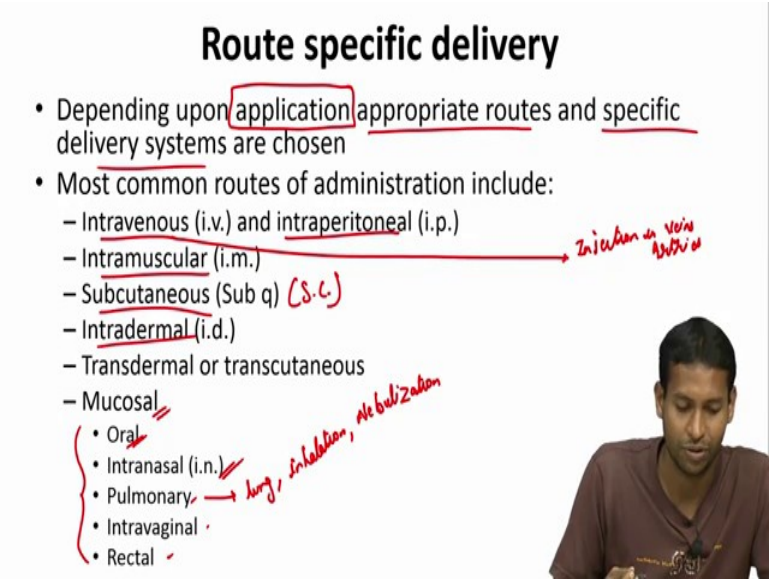

So, we are talking about route specific delivery. And again, the key point here, like in all sort of modules we have discussed so far, is that the route you choose depends on the application you are looking at. So, what is appropriate route and what is the delivery system that you are using is majorly driven by what is the application you are using it for. And we will go in quite a lot of detail about this in next few classes.

So, some of the most common routes that are used for administration are intravenous route. So, that is a sending nothing but directly injecting into the blood system. Injection in either veins or arteries and I am sure you all are very familiar with this particular system, most of the time when we are growing up we need to get vaccines, some of these vaccines are also given in all through these routes especially intravenous route. And the next is the i.p. - injection intraperitoneal. Again, very widely used in literature, and what it is, its essentially injecting it below your stomach cavity. So, it is between different tissue space where you just inject whatever you want to give.

Then if intramuscular, which as the name suggests is directly giving it in the muscles. So, typically you can use hip muscles, you can use biceps or you can use any kind of other large muscles, thighs, to inject this just because that ensures that most of it goes in the muscle than anywhere else.

Subcutaneous is nothing but just under the skin it is also abbreviated as s. c. And that essentially just means that you maybe lift up your skin and you just inject it below that, and that gets absorbed through that. And then you have intradermal which is nothing, but

is in the skin. So, instead of penetrating all the way through the skin you just penetrate somewhere in the skin, so that when you inject whatever is given is gets entrapped in that small skin layer through that which it can diffuse out of.

So, and then there other routes as well there are transdermal. So, and it is just something that you can just deliver through the skin and, so any kind of injection is essentially transdermal, but in this case, we are talking about just right under the skin very similar to subcutaneous route. And then you have any mucosal route, which means that that route has some kind of mucous that is experienced when you are injecting it. So, this could be oral. So, our oral cavity, our oral route is completely filled with mucous everywhere. So, there is mucus in our mouth, there mucus in our stomach and intestine. Could be intranasal. So, you can deliver things, especially, if you are looking to deliver things to brain intranasal is use quite a lot. You have pulmonary, again our lung is full of mucus and this is nothing, but delivery to the lung. So, this could be either through inhalation or nebulisation. Could be intravaginal, could be rectal. So, all of these routes have some sort of mucous layer that is experienced while injection or while administration. And so, again, we will discuss most of these routes in quite a lot of detail as we go along in this class and the next.

So, these are essentially giving you a laundry list of different administration options and there could be others as well. You have taken eye drops and that is nothing, but essentially you are giving intra optically. So, there could be other routes as well, but these are some of the major routes that are being used.

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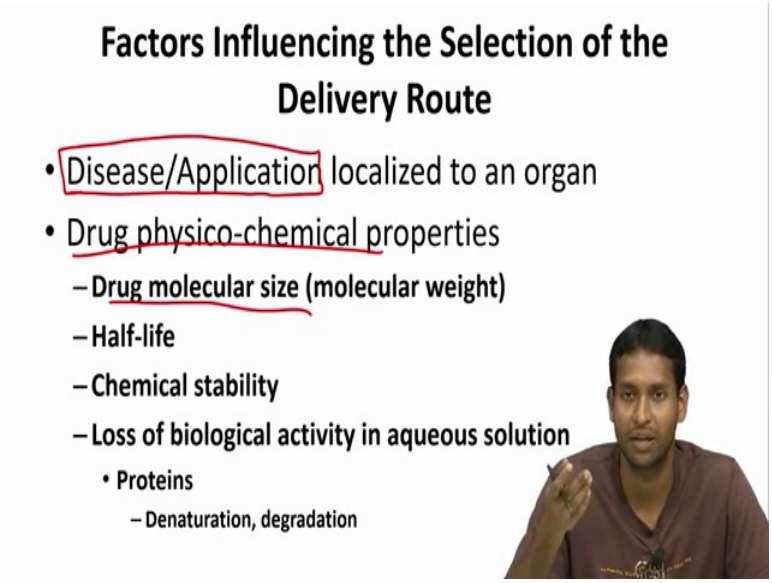

So, what are the factors that influence the selection of the delivery route? So, we have already talked about application is the major criteria. So, if it is, let us say, if it is a disease that is only on skin. There is really no point in giving an IV, if you can give it just topically onto your skin. Similarly, if the disease only localized to lung maybe giving it through a pulmonary route might be better than again giving it throughout the body.

Then it depends on what is the drug you are using. So, whether that drug is going work in that route or not. So, let us say again, taking example of the skin. Let us say if a drug is not able to diffuse through the skin, then there is really no point in giving it on the skin. If you want that drug to go all over the body, there is really no point in giving to the skin if the drug cannot go through the skin. And then similarly, so the drug physic-chemical properties become important if the drug is let us say insoluble in pH of 2-5 where which is what is going to experience when you take it orally, again there is really no point in taking that drug orally, because most of its going to precipitate out.

And this again involves a lot of things. So, what is the drug molecular size? So, how big the drug is essentially? What is the half-life in whatever route you are giving it, so maybe it gets cleared very quickly. How much stable it is? Again, if it is not stable at a low pH or if it is not able to penetrate the skin maybe gets degraded by the enzymes present in the skin, you need to consider all those factors. And whether whatever aqueous solution it experiences this goes back to the pH, whether it causes denaturation or degradation of the proteins that you are administering.

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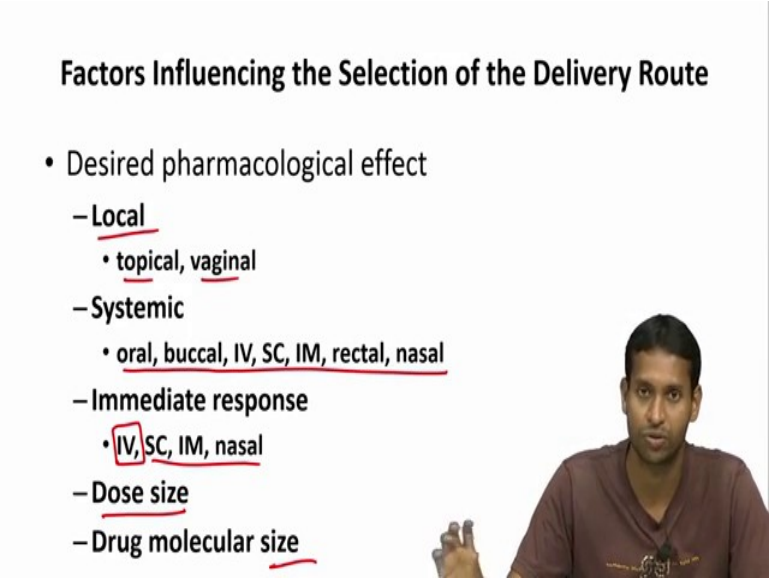

And then of course, it also depends on what is the desired pharmacological effect. So, as I said if it is something that is localized to lung and you do not really want to give it systemically. Similarly, if it is something that requires quite a heavy dose of the drug, let us say, if I need to have let us say grams of the drug, it is not going to go through the skin very well.

Then again, if the desired pharmacological effect is local so, like topical, vaginal these are some of the routes that can come in. If you want it to be everywhere, so let us say if its paining throughout the body or if its fever throughout the body, you may want it to be systemic and in that case any of these routes can be chosen. And if you want immediate response so, again if you apply something on the skin, it may take some time to diffuse in and actually reach the site where it is going to act and so that may take some time. But if you want some immediate response to happen the best route is the IV because that will essentially mean it distributes everywhere in the body within few seconds, and then other routes can again also be used if you want immediate response.

And again, we talked about this. So, what is the dose size? So, if you want quite a bit of dose to be delivered, maybe you cannot inhale that much amount of dose, maybe it is hard for you to inject that much dose in the muscle then you may be looking at intraperitoneal route or maybe oral route. So, all of these play a role and then of course, the size which is going to define a lot of physio-chemical properties, so if the size is let

us say too big it cannot penetrate through your skin layer and so that all affects ultimately what is the delivery route that you should choose.

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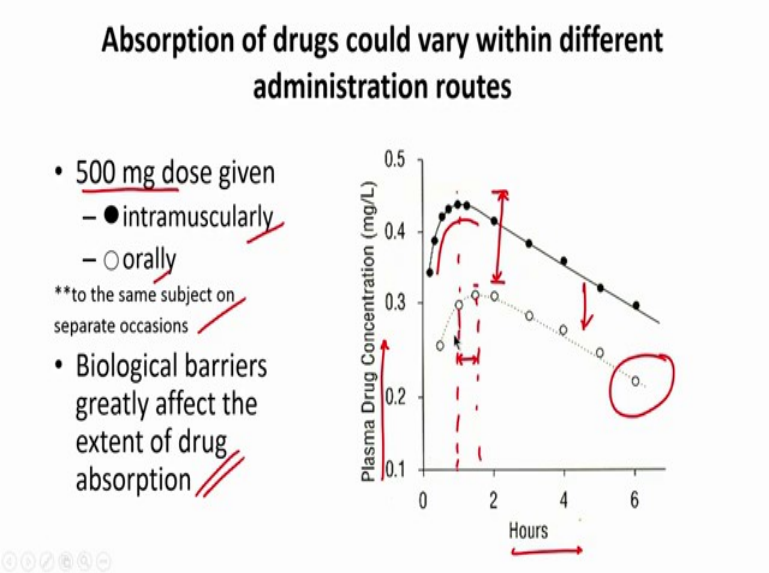

So, just an example of how different administration route can be. We talked about a similar case at the very start of the course. But let us say you have 500 milligram dose of a drug that is either given orally or is given intramuscularly to the same subject on separate occasions and this is an actual clinical data. And so what you typically see is that the plasma concentration of the drug is being reported here with time and what you are seeing here is when you are giving intramuscularly, you get a very high plasma concentration and the peak is also a little earlier than when you are giving it orally. So, this is the peak for oral, this is the peak for intramuscular.

So, first of all you see that there is a big difference in the peak value that you can get and then secondly, you can see that there is a time difference also. So, intramuscularly is able to have a lot more concentration of the drug at earlier time point then let us say oral. So, even though the same order drug is given in you see differences. So, that is why it becomes very important to choose a good route before you start your procedure.

And again, these biological barriers will affect your drug absorption. I mean obviously, we have discussed this previously, that the oral route is has lots of challenges the drug get destroyed in the gut there is absorption, then there is the first pass metabolism all of

these things will lead to lower amount of drug being present when you give the same drug orally compared to intramuscularly.

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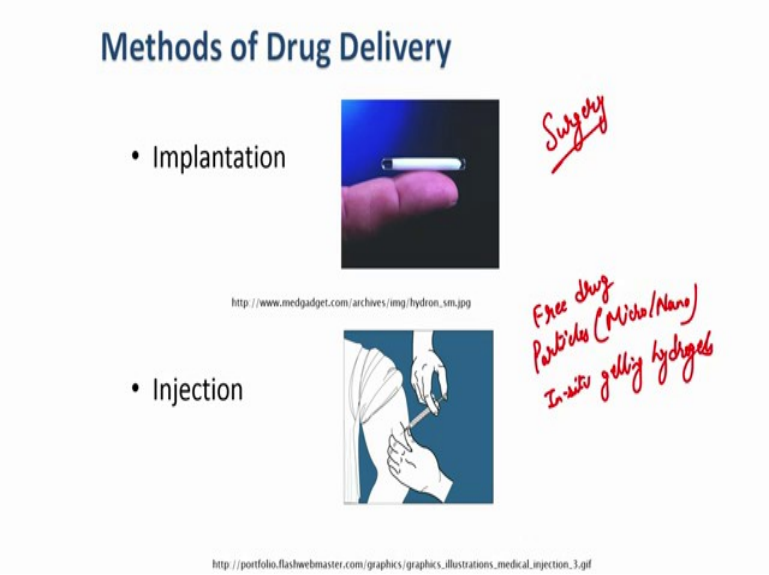

And then methods of delivery are important. So, whether it is going to be implanted or its going to be some other route. So, if it is implanted you are looking at a big implant, by big I mean something that can be used for a surgery or something like that. So, you are looking at some macro device or this could be injections. So, you know you required you do not really require surgery, but you would still require some sort of procedure to be done. This could be small particles.

So, again micro and nano, it could be free drug actually which is what is currently done very widely in the literature or this could be in-situ gelling polymers. Let us say in-situ gelling hydrogels which once they go in, they will form a depot at that side. So, or this could be again implantation which will essentially involve surgery. So, all of these factors need to be taken into account when in trying to develop or trying to administer a particular cure to a patient.

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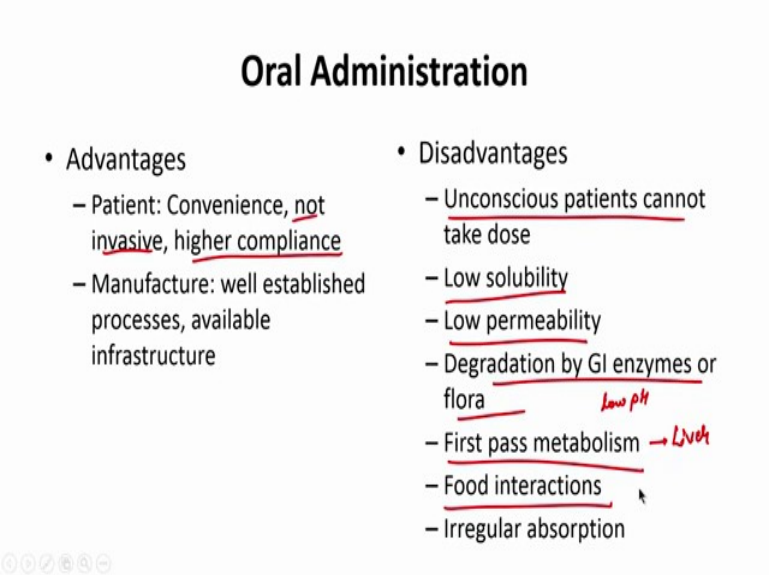

So, let us talk about oral administration one of the most widely used method. So, what are some of the advantages? One of the advantages is its very patient compliant. So, again we have all taken drugs orally, so all you have to do is just take a tablet, drink some water, and you have done for that particular time. So, it is a very high patient compliant very non-invasive method.

The manufacturing facilities are well established. I mean this has been done for now several decades and there is a quite a lot of literature and quite a lot of industry-based setups that can help you produce these tablet us in very mass number. So, that is always good because then you can take your cure to a lot more population.

What are some of the disadvantages? First of all, unconscious patients cannot take it. So, the patient is not awake it would not be able to swallow or eat it. It has fairly low solubility it has to go through very different ranges of pH and all. Low permeability, so even if you are able to get to your gut not everything is going to get adsorbed some of its just going to get excreted out.

A fairly harsh environment, so there are lots and lots of enzymes that are present that is going to cause it to degrade, there is low pH as well. So, all of these are an issue. Then you are talking about first pass metabolism, which is basically liver. Even before it is gets circulated into the blood system most of your drug may get metabolized by the liver during the first pass metabolism through the hepatic portal vein.

Then you do not know how it interacts with the food. So, maybe if you have just eaten the food the pH is different, the environment is different, there are less enzymes whereas, if you have not eaten the food for past two three hours then you really have no food in your stomach and your intestine, at that point the interactions on the food will be fairly variable. And that is the problem because then you do not know how much of the dose you have given. Whether the dose you have given is lower, then what should be whether it is exactly what it should be or whether it is much higher and you might reach toxic levels and with that particular dose. And then of course, there is a regular absorption, so it is fairly variable, that is a major problem here.

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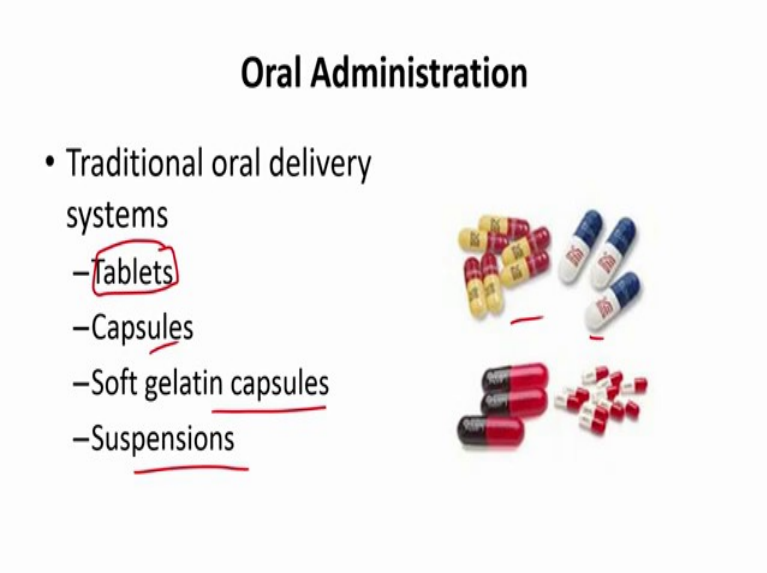

So, again here are some of the traditional oral delivery systems. So, I am sure you have seen all of these. So, you have tablets, one of the most widely used, you have capsules, you have gelatin capsules as well which are slightly different in characteristics, and then you have suspensions like cough syrup and things like that that you directly ingest.

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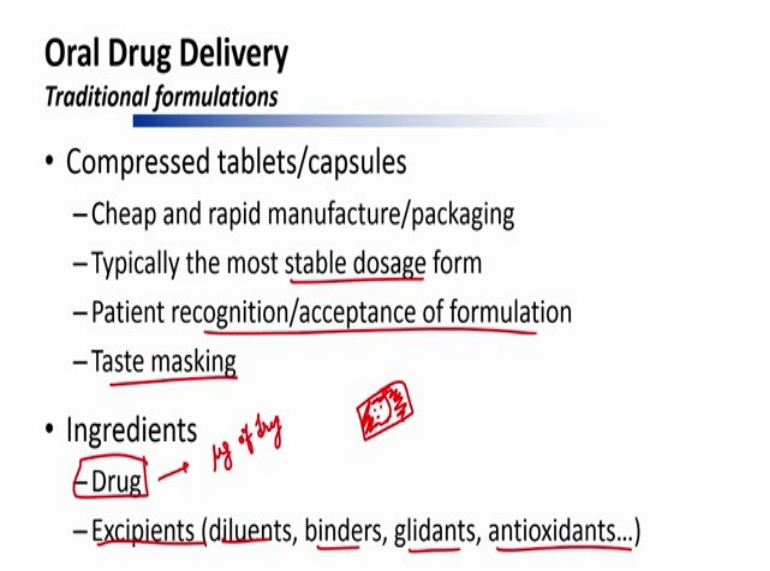

And so typically to form a tablet some of the traditional formulations is extremely cheap and rapid to manufacture and package this. It is it is in dry formulations its typically very stable. So, that is one of the advantage of a tablet that you do not worry about it just all dry. Typically, you will find that the biomolecules when they are in water they are more prone to degradation and losing their activity then when they are in a dry format.

The patients recognize it accept it, so the patient compliance is fairly high and it is all in and there is all kinds of processes that are present in there. And then there is a taste masking process as well. So, if let us say your tablet is extremely sour or something that is not a good tasting tablet then you can mix some good tasting molecules in there. So, that your taste can be masked and actually patients are okay in taking that tablet through oral route as well.

And, so it involves obviously, two major components one is the drug itself. So, whatever drug you are giving and then the next is the excipients. So, these excipients could be of several types this could be diluents to sort of make it bulk let us say if you only require a microgram of drug, then they cannot make a tablet out of microgram of drug because a microgram of drug will not be even visible if they make a tablet out of it.

So, what you do is you then make a tablet which contains this microgram of drug and everything else is sort of a filler. So, it could be a dilutent and it could be a binder, it could be a glidants anything in that sorter or maybe you want to give some more

functionality to it, so you are adding some antioxidants to it as well. So, the patients are more likely to take them as well.

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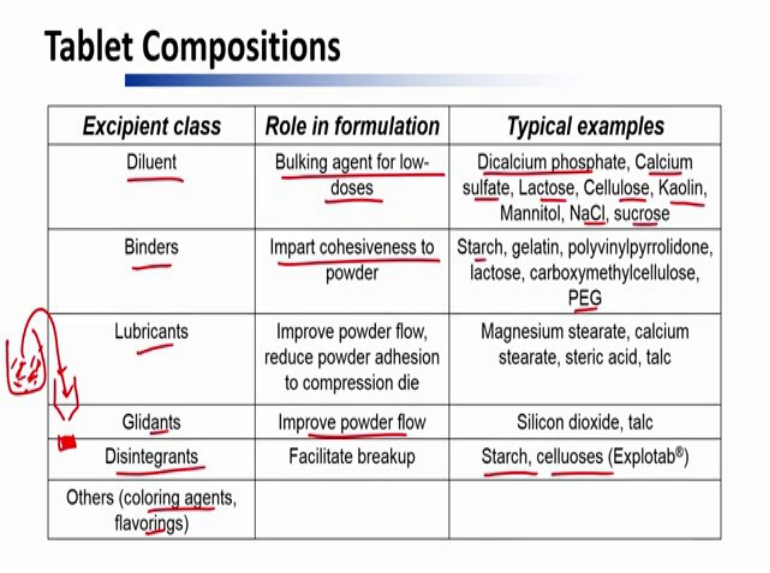

So, here are some of the examples. So, you have diluent which is essentially is a bulking agent for low doses as we just talked about it and here are some of the major compounds that are being used as diluents. So, it could be salt, it could be sucrose, also improve the taste lactose cellulose all of this is actually use the diluent quite often.

And then you have binders. And what do you mean by binder? So, essentially if you just put salt the salt is not going to form a tablet. So, you have to put some things in there that holds the whole tablet together. So, that improves the cohesiveness of this powder. And again, there are several examples of this you have starch, PEG and several other molecules it can be used for this. Then you have lubricants. So, lubricants are not really required once the tablet is formed, but before the tablet has found you need these lubricants and these glidants which will help in the flow of the powder, and this is required because when the tablet is being formed the tablet is essentially first in powder form and then this powder has flowed into a sort of a mould.

So, maybe if let us say this is my reservoir of the powder, it is then flown through some nozzle into a mould which is going to take the form of a tablet. But for it to flow well, because you do not want this powder to be very sticky. So, for it to flow well you need to add these lubricants and glidants, so that it can be rapidly scaled up. Then you have

disintegrants. So, essentially once you have taken it up you want this tablet to break up very quickly. So, you want something that once it goes into the stomach environment it either dissolves away completely or breaks down completely, so you then add those things as well.

And then of course, there are flavouring molecules that we briefly talked about, so maybe you want to improve the taste, maybe you want to increase patient compliance, especially in children you want to add coloring agent to help companies distinguish as to which product is for what applications. So, all of this can be then adapted.

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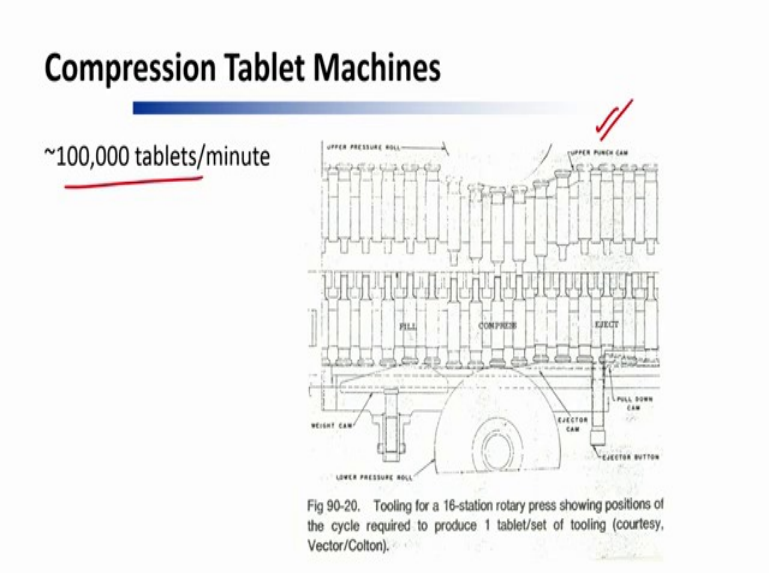

So, here is briefly what I was basically talking about before. So, here is a typical tablet machine and you are using some compression and filling to form these moulds and this again this technology has been used for quite a bit of time and its very well established up to the fact that you can make 1 lakh tablet us per minute. And so, in terms of scale up this is not a problem at all.

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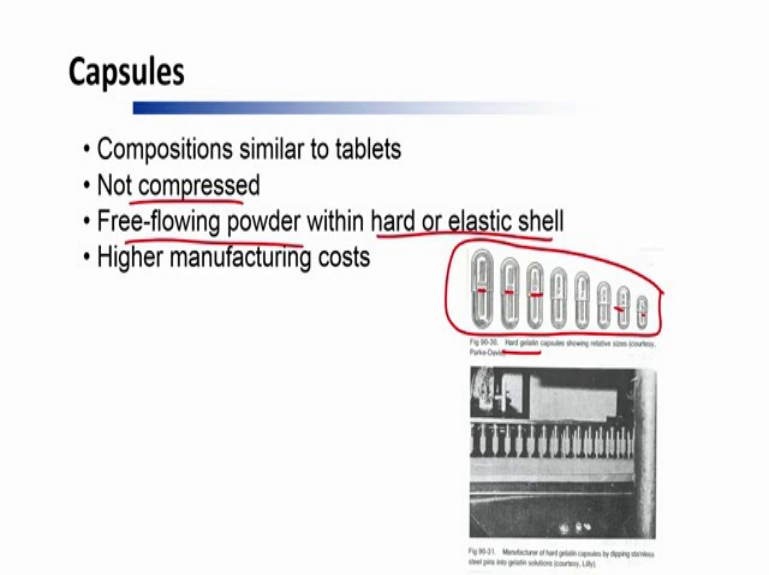

And then the similar thing for capsules the compositions again very similar to tablet, but they are not compressed. So, if you have ever opened the capsule you realize there is some free powder and so it is a free flowing powder within either a hard or elastic shell obviously, the manufacturing cost goes up because now you are using quite a lot of material and it is a little more cumbersome I will say a tablet which is just compressed. But if your drug is not very stable in that compression in the high pressure in those cases capsules become important.

And again, you can get them at various sizes each of these size has their own code. So, you can see them triple zero, double zero, and all the way up to five. And again this just defines as to what is the relative size and then there is also hard gelatin, soft gelatin that you can use as elastic shell for these capsules which will then once it comes in contact with water they will essentially degrade or dissolve away.

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

Thank you.