**Drug Delivery Principles and Engineering**
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**Lecture - 36**
**Route Specific Delivery Oral Route – II**

Hello everyone. Welcome to another lecture of Drug Delivery Engineering and Principles. My name is Rachit and we are going to continue our discussion on this topic.

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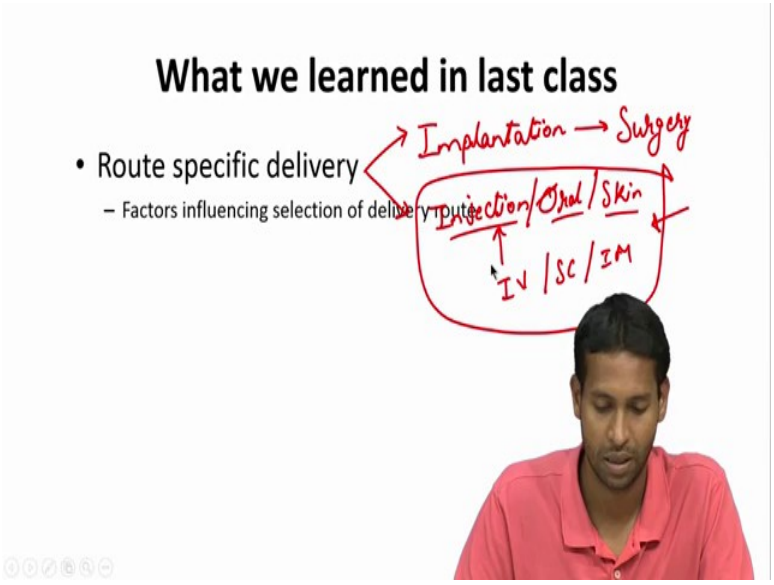


So, let us do a quick recap of what we learned in the last class. So, what we learned in the last class was first was route specific delivery which essentially has two different broad categories. One is implantation which means that there will be some surgery involved and this is in cases where it is too big, so your implant could be in millimeter sizes, in centimeter sizes and you cannot really inject that and another is, of course, injection.

And in this case the route becomes important or injection or it could be some other route also. So, it could be oral, it could be on the skin. So, even those which have big delivery vehicles they can also be delivered both through oral and as well as skin. But for the most part then we are looking at injection, which will then involve either an intravenous injection or a subcutaneous injection, intramuscular and several others.

And so, when we are talking about the route specific delivery basically it concerned about this section, because implantation again you can do at any point of time, but then surgery is much more invasive and that then becomes defined by what is the application and why you want to do a surgery. But for more traditional and more advanced systems we are more looking at injection because this is more patient compliant and depending on what route we choose we can get it to various parts of the body.

And in that we then talked about various factors that determine the selection of the delivery routes, essentially whether you want to deliver it to a local organ or multi organ, whether it is some property of the drug that may hinder it through a particular route. Let us say where drug is not very stable at low pH, then there is really no point of using the oral route. So, all of these factors we discussed in the last class.

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Then we focused on oral administration first and we talked about some of the traditional ways in which oral delivery is done. So, these could include capsules and tablets and also suspensions such as your cough syrups and all. And then we talked about that these manufacturing processes are well established, we can go as high as to let us say one lakh tablets per minute in that throughput range, so it is not really difficult to scale this up. But then it of course, has its own disadvantages where unconscious patient cannot take it, the drug gets destroyed quite a bit with that harsh environment, it faces the absorption is fairly low.

So, we will talk more about how we can now improve these different challenges and make sure that drug is delivered more efficiently. So, let us dive into that, ok.

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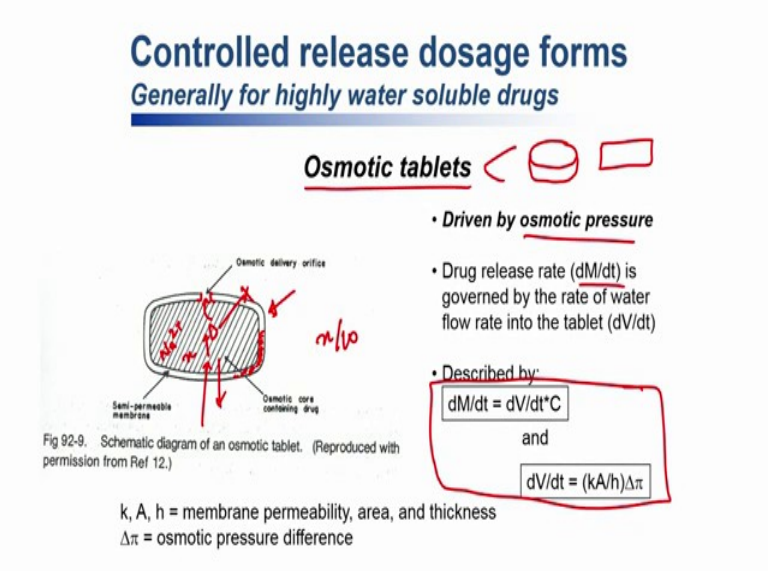


So, the first thing we are going to talk about is related to the controlled release and these are called osmotic tablets. So, these are nothing, but what your standard tablet looks like. So, maybe it is a tablet something like a centimeter long and could be in different shapes as well, and the distinguishing factor of these osmotic tablets when you compare them with traditional tablets that we have talked about is that these are nothing, but a mini pump. And so, let us see what we have here.

So, in this tablet is if you zoom into this tablet you will find that there is a small hole that this tablet harbours and then there is a semi permeable membrane also containing a lot of ions inside along with the drug. So, even though from the outside it looks like any kind of traditional tablet this is nothing but an osmotic pump.

And so, how does the release happen from here? So, this is driven by osmotic pressure. So, the drug release rate is going to be nothing, but dM by dt is going to be governed by how much water then goes into it. So, here is a semi permeable membrane which will allow the water to go in and out, but that drug inside cannot come out from here, it can only come out from these pores.

Now, what will happen? If you have packed this particular tablet with lots and lots of ions, so let us say you have concentration of sodium inside at x and maybe the outside is only x by 10 then the water will have tendency to move in because there is an osmotic imbalance. And we know that we can actually use van't Hoff equation to determine what will that be. So, this is going to be described through this mathematics and from that you can then start to understand as to how this is going to work. So, what will essentially happen is that the water will move in, it is going to create more and more pressure for this drug to go out and whatever is inside to go out from this small orifice and that is going to drive the release of this drug from these osmotic tablets.

So, again this is a fairly nice system that we talked about here. What will happen is instead of releasing the drug immediately when it goes to your stomach where the environment is harsh this tablet is going to protect the drug inside through this final coating on the outside. And only when slowly the drug is going to be released when the water is moving inside. So, you get a little more prolong release. So, it is not some of the drug delivery systems we had talked about where you are getting as much as weeks to months, but in this case, you will get a control release for over a period of 20 to 24 hours.

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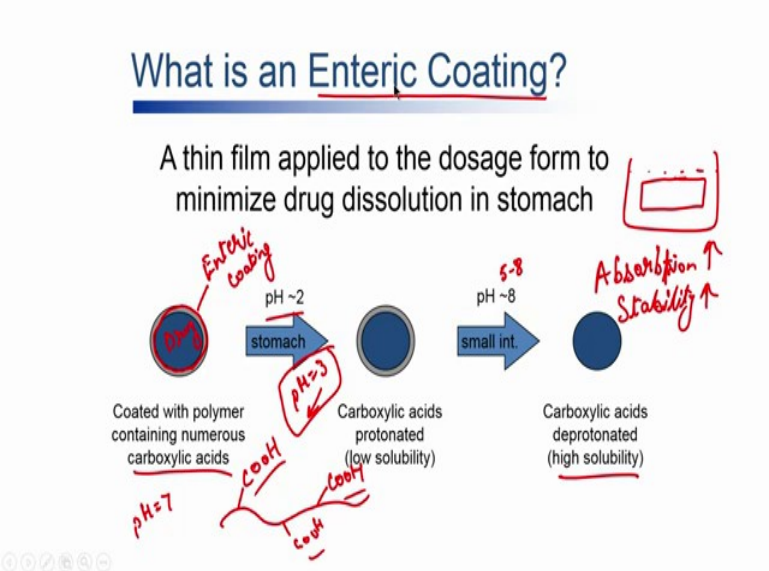


Let us talk about another strategy that is very widely used which is enteric coating. So, what is enteric coating? So, typically a thin film is applied to the dosage form to minimize the drug dissolution in stomach. So, let us say again going back to the

traditional tablet, let us say this is a traditional tablet. Once this tablet hits water this tablet starts to dissolve away immediately and regardless of whether this is in stomach or whether this is in mouth that is why sometimes when you take the tablets you can even feel that taste of the tablet, this tablet will start to dissolve away and release whatever is encapsulated inside.

But again as we already know that the harsh environment present in the stomach is going to destroy a lot of this drug. So, to prevent some of these things from happening we apply this coating which we call as enteric coating. And what these coatings do is they are insoluble in stomach, but as you move further down in from the stomach to intestine these coatings then dissolve and then release the drug. So, it sort of acts as protector of the drug in your stomach environment, but when you are going further down these coatings then dissolve away and the drugs can then release.

So, this is just a graphic showing let us say this is drug, then you have enteric coating here and these are nothing, but these are polymers that contain quite a bit of carboxylic acid and I am going to come in a moment as to why these act as good enteric coatings. So, at pH 2 which is typically found in stomach these carboxylic acids are now protonated. So, let us say this is the polymer chain and that contains a lot of carboxylic acid. So, all these carboxylic acids will have a certain pKa at which these will be protonated in a sudden and below and above that this will change charge.

So, we all know that a neutral pH, let us say the pH is 7, then these particular molecules will exist as COO minus they will lose their proton. But once the pH drops below their pKa let us say at a pH of 3 these will then get protonated and exist as the carboxyl form.

Now, we know that ionic form of a polymer is much more soluble then the non-ionic form which is what it is at this stage and so its solubility dramatically drops. So, we use a polymer whose solubility is fairly low in non-ionic form and the solubility increases in an ionic form, what we will have is at a pH of below 3 for this particular case this will be an insoluble coating. So, this will be an insoluble coating it will not let the water and the harsh environment penetrate through, but as it leaves stomach and goes to let us say all the way up to the pH of 8, does not even have to be pH of 8 it could be even pH of 5 in this particular case.

So, once it let us say goes to a pH of 5 to 8 in the small intestine these carboxylic acid containing polymers will get deprotonated will have high solubility and will dissolve away. So, that way now that drug can release. So, what you have done is, you have ensured that your drug is not releasing out into the harshest environment for the drug. And it is actually releasing out in the intestine where the absorption is going to be maximal anyways. So, that is what you want when you are taking the tablet orally that it absorbs into the body. So, the absorption is also going to improve, as well as the stability of the drug is going to go up. So, that is where the enteric coating comes in. So, that is one of the engineering strategies people use.

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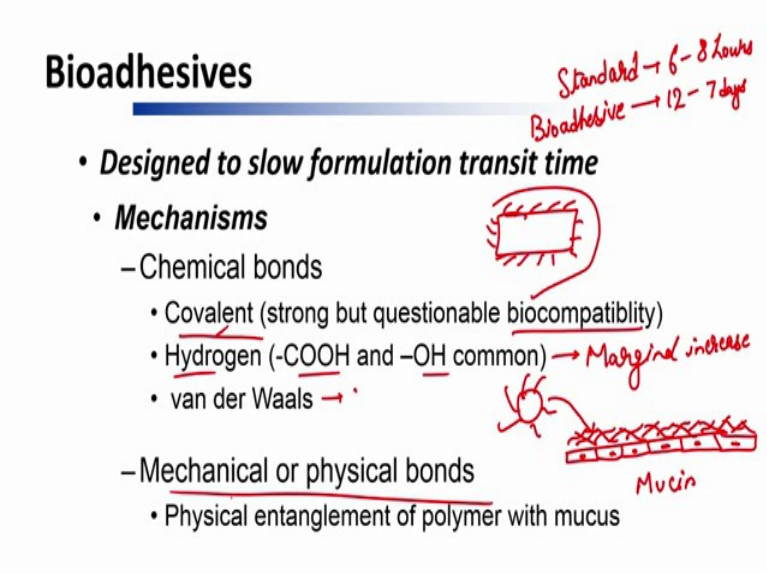


Then there is another strategy it is called bio adhesives and let us see what these are. And so, these are nothing, but these are formulations that slow down as they transit. So, typically let us say if you take a tablet the tablet dissolves and is dissolving throughout your oral route process. A tablet will dissolve and then release most of the stuff within let us say 6 hours. So, let us assume that a standard release in within 6 to 8 hours, but then as you make these more bioadhesive, what you can have is that is that the standard time of the drug or let us say the bioadhesive time could be increased all the way to 12 hours all the way up to even 7 days. It depends on how good you can get these coatings to be.

And so, what is the mechanism here? The mechanism is that you can form either covalent bonds or chemical bonds. So, these could be covalent bonds, essentially

meaning that let us say if this is your tablet, maybe it contains functional groups that are fairly reactive. So, maybe these functional groups go ahead and bind to your stomach or your intestine lumen and that increases the time instead of just going out all the way down to the intestine and they just get stuck at one of those walls and form a covalent bond.

The problem with that is there is always questionable biocompatibility because if these groups are so reactive then they can also react with some important receptors; important proteins that might be needed for your normal functioning. So, this is not usually strategy people adopt. Then there is another way, you can form hydrogen bonds. So, again things like carboxyl and hydroxyl are common. The problem with the hydrogen bonding is this does not really increase the residence time, its very marginal increase because these are weak bonds and do it with the flow with time these will break and the cargo will keep on moving further down and down.

And then of course, you can do van der Waal forces as well they are better than the hydrogen bond in terms of their strength because the several of them. But again, they also show not a very high increase in the residence, so maybe slightly better than the hydrogen bonding, but still not as not sufficient to get it up to the period of days.

The other way you can go about it is to form mechanical or physical bonds. So, this could involve just physical entanglement of your polymer with the mucus. So, if I zoom into let us say a layer wall of your intestine, these are intestinal cells and they all secrete mucus. So, what happens is, mucus is a combination of lots of polymers and when I say polymer in this case these are proteins. So, one of the major protein is mucin and these are long molecular weight chains that are being secreted and essentially forming a gel.

So, what you can potentially do is if you have bigger chains sticking out from your cargo, they can potentially go in and entangle with these mucin chains and that may cause significant slowing down of this as the progress and formation of some physical or mechanical bonds. So, that is one strategy.

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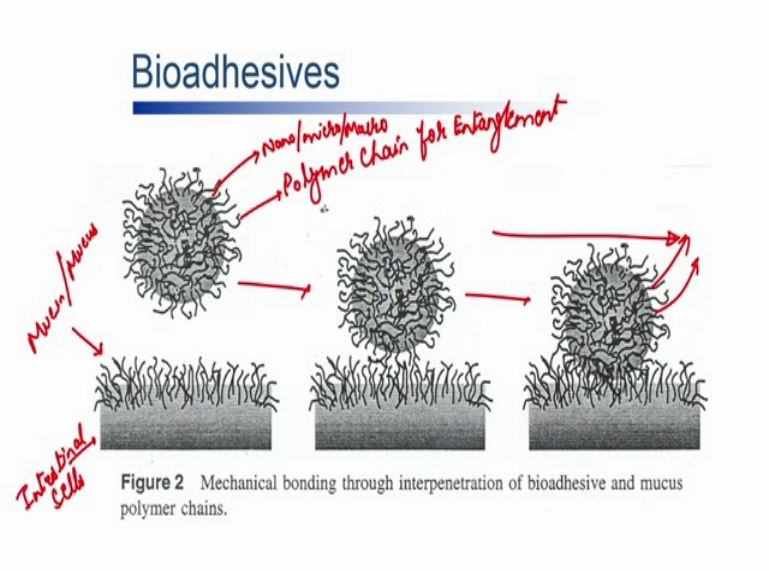

Figure 2 Mechanical bonding through interpenetration of bioadhesive and mucus polymer chains.

So, this is just pictorially shown here. So, in this case this could be considered as intestinal cell. This one you can categorize as mucin or mucus. And here you can talk about delivering any kind of nano, micro or even macro particles with lots and lots of polymer chains for entanglement. And what we expect to happen is that once these brush like nanoparticles or micro particles touch these mucin surfaces, these polymer chains will start interacting with it and get entangled and that will allow it to remain on the surface even under the flow conditions that it may experience in intestine. So, that is another way you can increase the residence time of your drug or your particle formulation and then this can then slowly release it over time, and you can potentially get release much higher than 6-7 hours what you typically get when you take a tablet.

So, even with all these you do not really see much enhancement, you get some minor enhancement with any of these strategies, some work better than the other, but even then mostly you are talking about maximum of maybe a couple of days that will be able to get with any of these strategies.

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So, let us discuss a paper which has used some of the similar strategies to increase a residence time by quite a bit. So, this is a paper that was published about 3-4 years ago and its titled oral and ultra long lasting drug delivery system especially for the oral route and this is directed toward malaria elimination goals.

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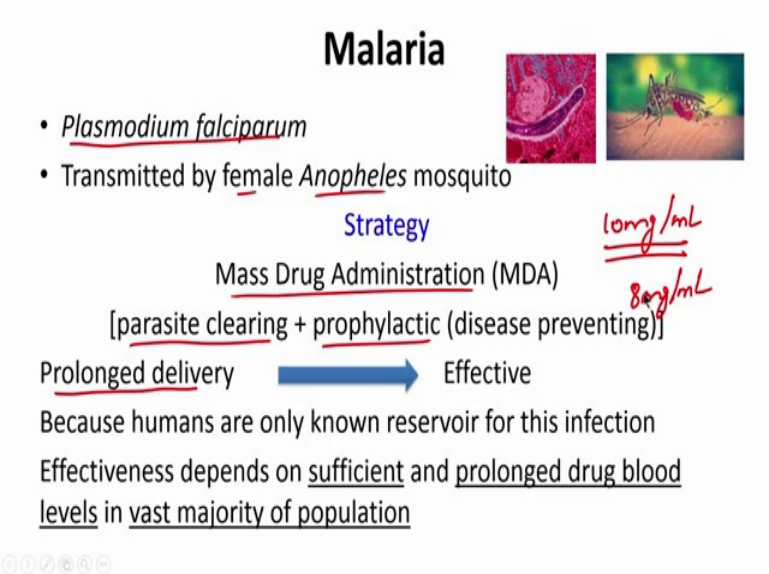


So, let us see what the authors have done. So obviously, as I just mentioned this is targeted to malaria. And the major organism that is responsible for causing malaria is plasmodium, that is a picture of a plasmodium worm. And its transmitted by a female mosquito which scientifically is known as Anopheles and that is a picture of that particular strain of the insect that transmits it.

And so, the strategy which is typically adopted in cases of malaria is to do a mass drug administration. And what that means is you administer it to lots and lots of people especially this thing is fairly common in Africa, where this is very prevalent, you take the whole population and you give this drug in mass to all the people whether they are infected with the malaria or not.

And what they does is it causes the parasite to clear from the people who are infected, it causes the prophylactic prevention as well. So, let us say if I was going to bitten by this mosquito and if I am already getting this drug then even though I might get bitten by this mosquito this worm will not be able to survive in my body. And then not to mention, when you do this in the mass scale all these drugs will go out in the environment as well and also make sure that some of these worms are also dying in the environment.

And if you if you do it for quite a long-time at least the results have shown that it is fairly effective. Since humans have the only known reservoir if you can eradicate in humans this disease is going to get eradicated, but then again, the effectiveness depends on sufficient and prolonged drug blood levels. So, if you, for some reason let us say the blood levels required are 10 milligram per ml, let us hypothetically assume its 10 milligram per ml. So, you want to make sure that this amount of the drug remains in the blood for the duration of the course otherwise what can happen is even if it drops to let us say 8 milligram per ml that can allow mosquito and these pathogens to grow in and actually may even develop resistance against the drug.

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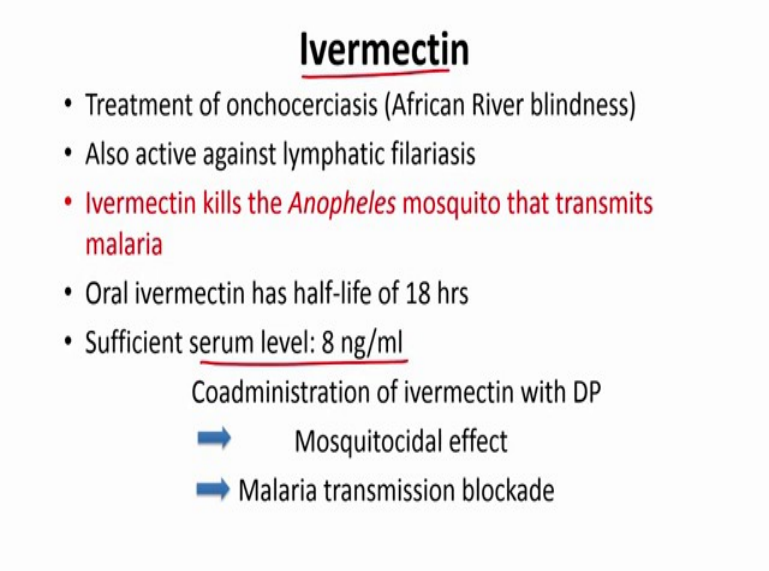


So, the drug that is very widely used is ivermectin and its used for treatment of African river blindness is also very effective in other diseases as well. This drug actually kills the anopheles mosquito that transmits the malaria.

So, the oral ivermectin has a half-life of only about 18 hours. If I take a tablet of this ivermectin, I will have to basically take another dose in another 18 hours and not to mention I have to take a very high dose first to get it to a level where even after 18 hours it remains above the 10 mg per ml that I just mentioned. And so, in this case the sufficient serum levels are not 10 mg, but 8 nanogram per ml. And then if you if you start administering it with other drugs you have mosquitocidal effect and also malaria transmission blockade.

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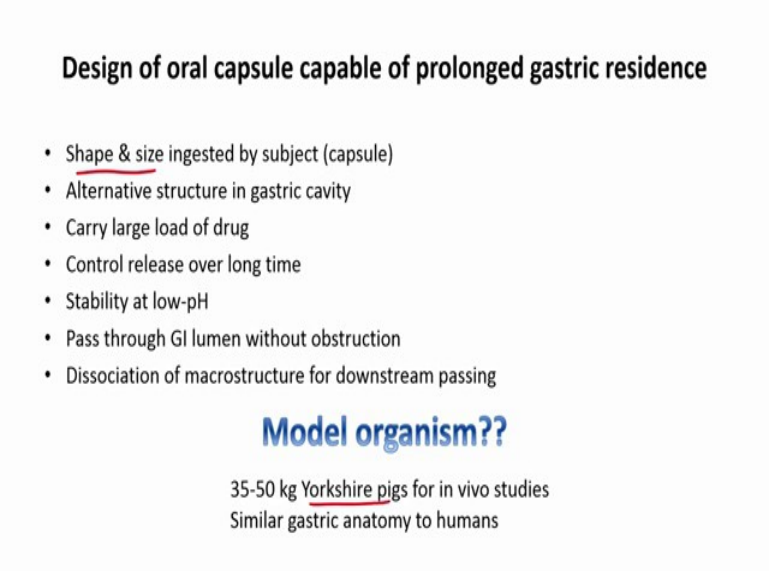


So, now the challenge is would the patient really take this drug if they are not suffering from this. So, that is a big challenge. And so, for that these authors here have designed an oral capsule and that can result in prolonged gastric residence. So, maybe once you take it that should be enough for you to for let us say about a week or 10 days or something. So, that will increase the patient compliance by quite a bit amount.

So in this case what they have looked at is they have looked at the shape and size of this particular capsule that can stay longer. So, they played around with that parameter and what structure they can use to have residence in the gastric cavity. It should also be able to carry large load of the drug, so that because if you want it to be there only for more than a week it should have enough drug. So, that it can be necessary releases the drug and the serum levels are higher for more than a week. It should be controlled release. You do not want everything release immediately or much later, it should be controlled.

It should be stable at low pH, so whatever system you have it should not really disintegrate otherwise it will not have high residence. And it should be able to pass through the GI lumen once you have done with it because eventually you do not want your stomach to get filled up with these things. So, it should also be able to be cleared out so, very similar thing.

So, what is the model organism that we can use here? So, in this case the authors have used Yorkshire pigs. Pigs are again we have briefly discussed before, are very similar to human in terms of the weights, in terms of their different tissue, architecture and sizes.

So, they are they are used very widely as models. So, in this case they have also used pigs of about 35 to 50 kg.

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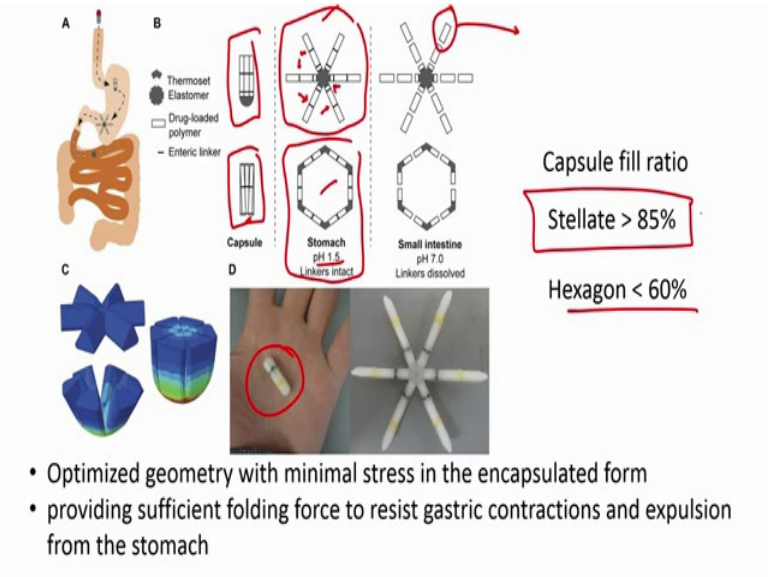


And this is the system that they have designed. So, they have designed a capsule which is packed initially. So, I just like any standard capsule as you can see here and can be taken orally, but once it goes in the stomach it opens up into these 6 branches as it is shown here. So, at a stomach pH of 1.5 or 2 it will open up like this. So, they have designed two structures, one is this structure and one is this structure. These are the two possible scenarios that the authors were looking at, and then eventually they have imparted some degradable components into these structures. So, these things can break out and that will result in them becoming much smaller so, that they can pass through the stomach.

So, here is a whole idea that you take this capsule, it goes in the stomach, at that harsh environment it opens up at low pH. It is big enough, so that it will not be able to go through here, but once it starts to degrade it can then come out. So, that is the whole point and then they have looked at various optimizations, so this stellate shape gave them about 85 percent more efficient packing in capsules so they can load more drug compared to this hexagon. So, they went with the stellate shape.

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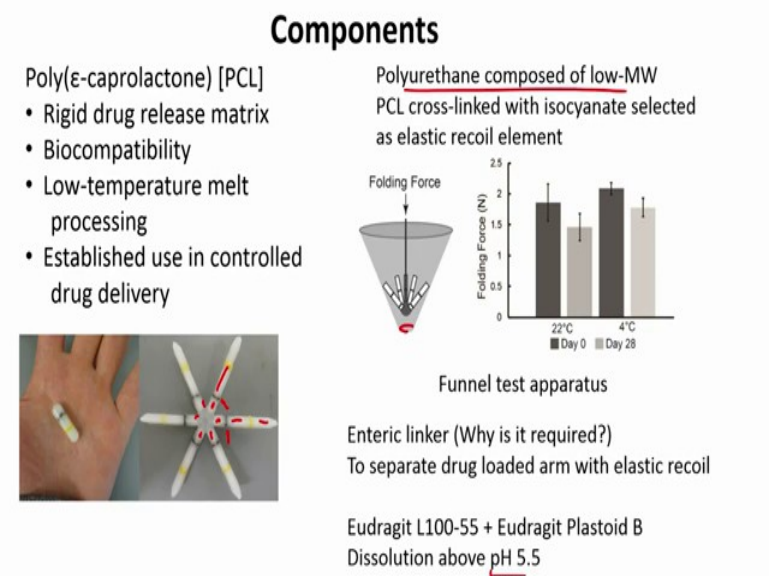


And then let us look at the various components. So, there is a PCL component which is polycaprolactone. And it is a rigid material for releasing the drug. It is fairly biocompatible, used quite often prepared by low temperature melt processing and that is what they have used. So, all of these components they have been designed from PCL.

Then they have put an enteric linker. And so, why is it required? This is to separate drug loaded arm with the elastic recoil. So, this is the elastic recoil and then they have put an enteric linker. So, that it separates out and the drug, so this is what we are talking about and then also that dissolves at higher pH. So, it will keep on slowly dissolving and once it reaches higher pH it will completely dissolve away, so that allows these arms to get cleared away from the stomach.

Polyurethane which is composed of low molecular weight PCL is used for cross linking. So, this is basically that recoil component and what they have also done is they have looked at the folding force that it might be required to pass through the pylorus which is nothing, but the stomach hole through which your food passes and goes to the intestine. And they have optimized these formulations such that the force that any object may experience its able to hold in that force should not really fold back. So, that is the whole criteria in designing this.

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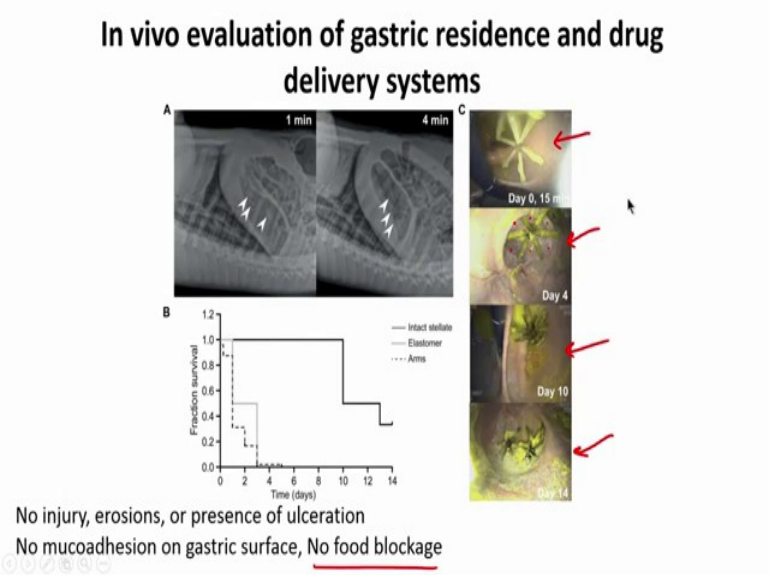


Then they went ahead and did some experiments on pigs and as you can see these things get lodged into the stomach as it can be seen from all these images and here is the residence time. So, if you give only arms those things clear off, if you give only the elastomers those things clear off, if you give it the whole combination with the arms, the whole intact stellate, that remains into the stomach for quite a bit of time.

So, here you can see its showing residence up to 10 days in 100 percent of the cases and then it starts to degrade and come out. And they further observed no injury or erosion to the animal. It was not adhering to the mucus. So, it is not like that is the reason for that and the major point was the safety. So, whether this is going to obstruct the food movement, but given its fairly porous, it did not really cause any kind of food blockage.

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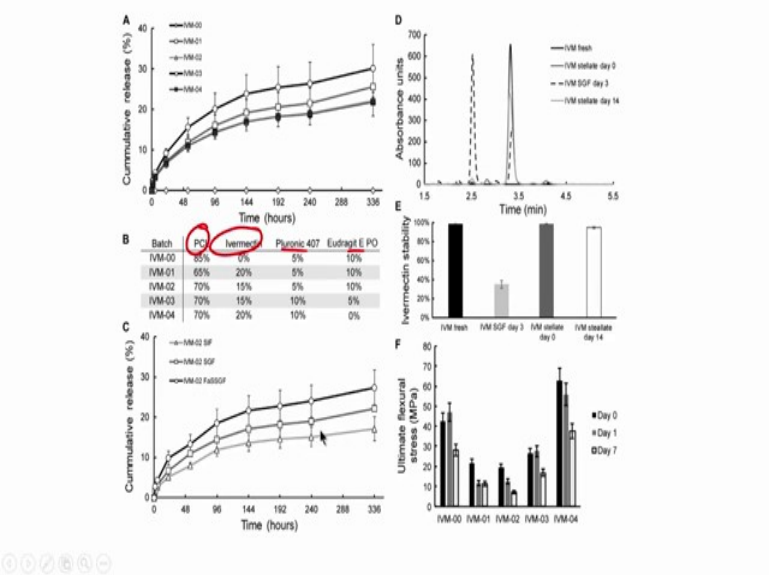


And then here they have shown that they can change the formulation, so they can change PCL, amount of the drug, different polymers that they are using there and they can vary the release as well. So, you can tune this polymer. So, this in this case they are trying to do it with ivermectin, but you can use any other drug which is also compatible with that system and you can essentially get different kinds of release rate. So, this is what they have shown here.

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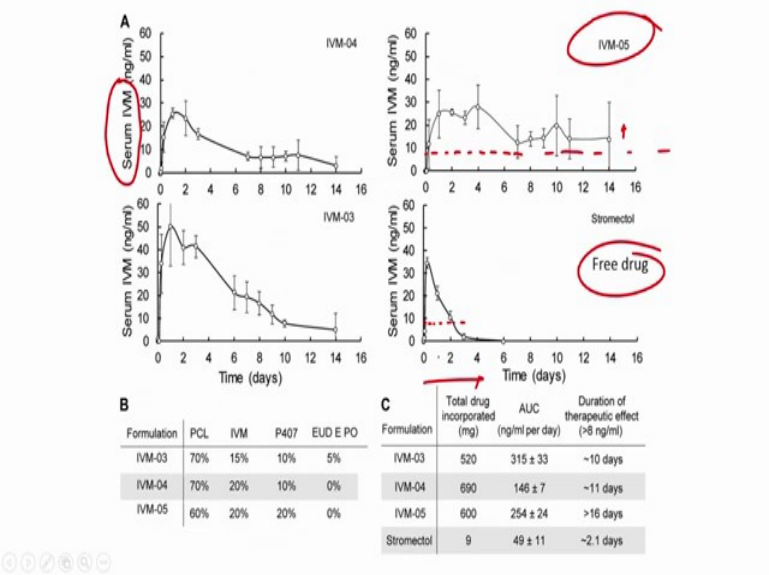


Then they have shown the serum levels of the drug. So, in this case the serum IVM with different formulations you can get different values. So, as we talked about its about 8 nanogram per ml and you can see let us say for example, of this case constantly let us say

if I draw a line at 8, then what you see is throughout the whole study you see much higher, at least for 14 days, much higher serum levels for this drug which is going to be much more effective. So, once you take this tablet you do not have to take it for next 14 days. And this is for the free drug. So, you can see it gets cleared out very rapidly, within almost two days you need to take another tablet.

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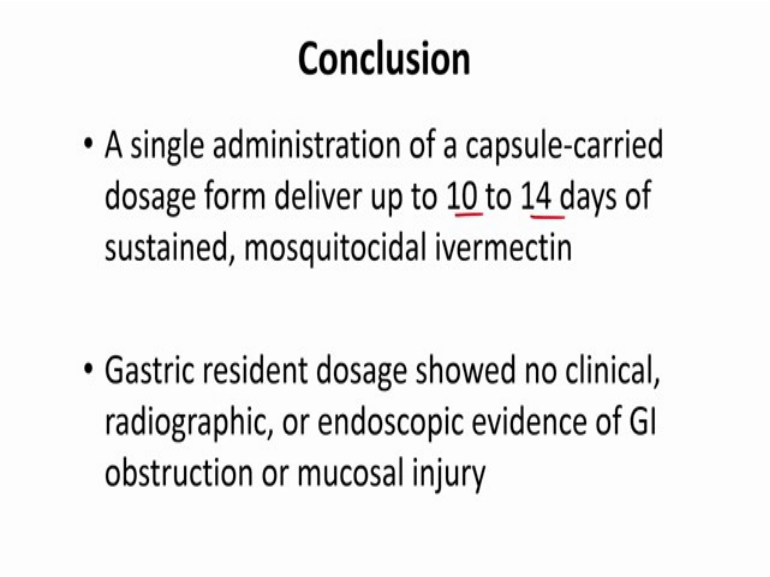


So, the conclusion these guys drew from this is that the single administration of a capsule carried by these dosage can deliver drug up to 10 to 14 days and sustain. As well as, at least in the pigs there is no evidence of any obstruction or mucosal injury once they use this system. Of course, this is at the research phase it still needs to get tested through quite a lot of rounds, this is just one example of what people are doing to innovate in terms of the delivery through oral route. So, lot of the testing will need to be done before it can reach clinics, but just a promising system that I wanted to discuss with you guys. So, we will stop here and we will continue rest in the next class.

Thank you.