Drug Delivery Principles and Engineering
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Lecture – 59
Responsive Delivery Systems – I

Hello everyone. Welcome to another lecture for Drug Delivery Engineering and Principles. We have finished our vaccine module and we are now shifting towards a different module which is more on stimuli responsive and targeted delivery systems. But before that we will just quickly do a recap of what we did in the last class.

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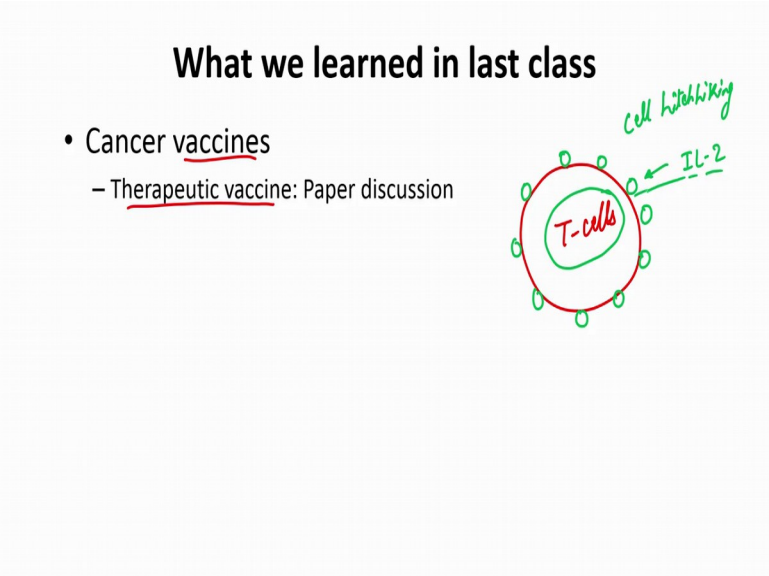

So, as I said we were discussing about vaccines and particularly cancer vaccines in that regards. So, we had discussed several theories as to what are the different vaccine types, for cancer, both prophylactic and therapeutic. Prophylactic is essentially just treating let us say a microorganism that is resulting in the cancer being developed. So, such as HPV or hepatitis B, but in therapeutic, it is more to treat the cancer which as we traditionally know to be quite a dangerous disease. So, that is to train the immune system against whatever mutations it has happened in the cancerous cells.

So, because there might be some mutations, maybe a protein that is responsible for normal apoptosis of the cell is now mutated or maybe it was causing enhance survival in harsh conditions. So, all of these mutations are foreign to the body, even though they are

very minor and it is hard for the immune system to detect them and so, there was the whole goal with cancer vaccines is to how do we is strengthen our immune system to be able to act even at that small minute level of changes and be able to kill the cancer cells.

And then in the last class particularly we looked at a therapeutic vaccine example that is being used in the research. This was an example in which the authors were taking T-cells and then these T-cells were being then loaded by particles in this case liposomal particles. And so, this is nothing but cell hitchhiking as we had already discussed quite a few classes back, in which the particles were tagged on to the cell membrane and then the cells were taking them to wherever they were going.

And then these particles were carrying various kinds of molecules. So, in this case we have seen an example of IL-2 which is something that stimulates T-cells and there are other receptors as well. And all of that what it does it activates the T-cell in the surrounding environment because now there is a high concentration of your activating molecule, and because of that these T-cells are now much more powerful in terms of dealing with what they find in the tumor micro environment. So, that was what we discussed in the last class.

Now, we are going to switch topic, and we are going to start our module on stimuli responsive, stimuli sensitive, and some stimulus that these delivery systems will respond to.

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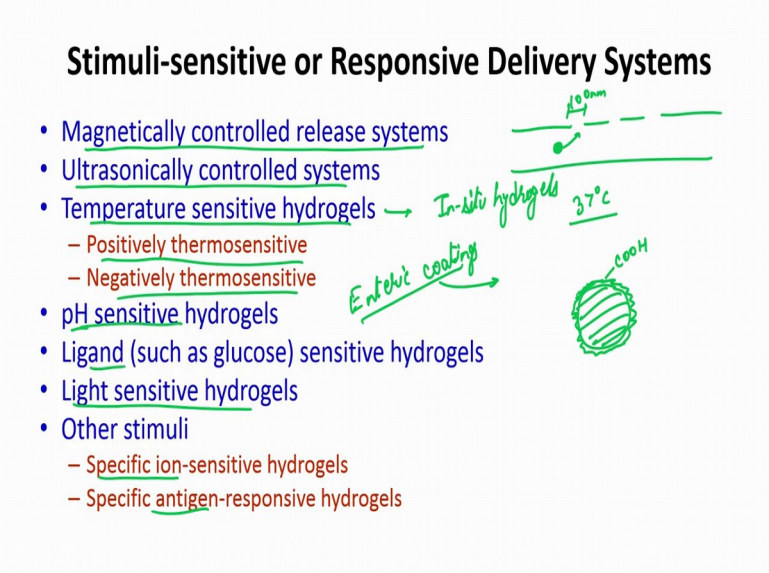

And this could be external, this could be internal some of these examples we have already done through the course we have talked about how these tumor environment have EPR effect which is enhanced permission and retention of the blood vessel. And so, that is something that we anyways used with our particulate system, we are saying that if we make 50 to 200 meter particle they will end up accumulating more in the tumor regions. So, if I say that these tumor vessels have gaps and these gaps are 100 nanometer, then 50 nanometer particles where anyways accumulating in these tumor regions because they can go through the blood vessel. So, these 50 nanometer particles will go and accumulate. So, these particles at anyways responsive to the tumor environment. So, that is one type of response.

But then we want to have more control over system, we want to have much more capability to be able to turn a system on and off when required, and if there is an external stimulus we can give, that will give us a lot more to do that. And so, that is what we will talk about, and then there are various systems like that. So, some are already listed here; so, when is magnetically controlled release system that means, that they will respond to a magnetic field and then and we are going to go into details of some of them. Then we have ultrasound controlled system.

So, if we can use these ultrasound waves to control our systems to either release molecule or change the properties, then we can have temperature sensitive hydrogels. Some of this we already talked about when we were talking about in situ hydrogels and we were saying that may be the trigger for the polymerization is 37 degree Celsius temperature. So, that is an example of temperature with sensitive hydrogels, but then we will we will learn some more about how further we can modulate this.

And then this could be either positive thermo sensitive or negatively thermosensitive and again we will talk about that as we go along in this class. Then we can think of pH sensitive hydrogels. Again these are some of the systems we talked about, not particularly hydrogels, but pH sensitive systems we had learned about enteric coatings. Remember, what were these? These was these were coatings that if you have a particle with a labile drug and if you coat with these polymers that are high in COOH content, then at low pH these are insoluble. And that is going to then protect your cargo and when the pH increases they will become soluble. So, these are enteric coatings.

So, this is something of a pH sensitive system. We will talk some more about this pH sensitive system and then these could be ligand sensitive too. So, maybe in presence of a certain ligands such as glucose or something else, these systems will do some change in property and cause release of the drug or again enhancement of cell attachment, some property that is desired in your disease application. These could be light sensitive as well. So, you can have light as a trigger for either bond formation or bond dissociation. So, all of this will change the release rate.

And then you can have other stimuli as well. Basically, what you can think of and then engineer with the current library of the products that we have in the market, you can have something specific to certain ion. So, maybe calcium, maybe magnesium, it may be certain antigen, so like ligand this could be anything else as well and all of this can result in a responsive or a stimuli sensitive delivery system. And we will see some of the examples here, but this is just a small list of examples that I will give you it just depends on the application you can make more there are several others in literature also that if you read through some journals you will find it.

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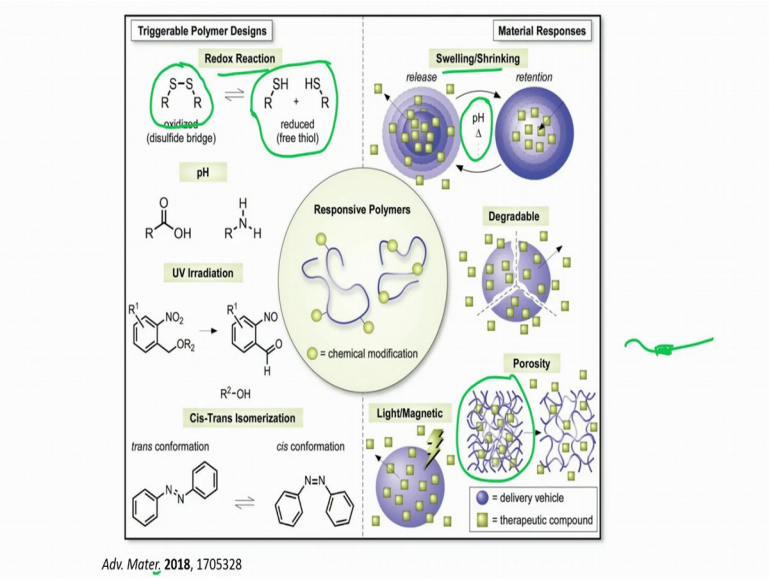

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So, here is just a figure from a paper from advanced material. And what you are looking at is some responsive systems. So, as you can see we have talked about swelling and shrinking on the basis of pH. So, these were through the ionic hydrogels if you remember, and the concept, there was you have put in maybe a hydrogel which contains

lots of carboxyls. So, what will happen if there are lot of carboxyls in this vicinity? That at low pH, all of them are carboxyl and are protonated. So, they will not lose their H plus meaning that they are neutral charged. So, they will have a certain pore size. But what happens if I now increase the pH and goes above the pKa of this particular acid, then what will happen, all of these will become negatively charged because they will lose their proton.

And now this negative charge will repel each other. So, because of that this pore size is going to increase. And we have already discussed this I am just repeating it for recall value. And so, this is nothing, but a system that is pH responsive it swells and shrinks. There could be systems that will degrade also in cer in presence and in trigger, it could be a presence of certain enzyme in the system which can degrade this bond, it could be just the environment may be pH itself.

Then you can have porosity can change. So, you can have light or magnetism causing degradation of the bonds. So, maybe there is a bond that is liable and cleaves in presence of light. So, if that happens then what will happen is a structure like this will change to a structure like this because the bonds are now broken, it is much higher porosity, causes much rapid release.

And then you have other responsive polymers as well, so you can have redox reaction happening. So, this will be responsive to the local redox potential. So, if you have highly reducing environment versus oxidizing environment, so if you are oxidizing environment it will remain as a bond like this, but if this molecule goes to a reducing environment, it will break this point. And once the bond is broken again the porosity will change.

So, all of this is just some examples you can have UV radiation to cause again bond breakage or bond formation. So, this will change the pore size and what not for your drug delivery system.

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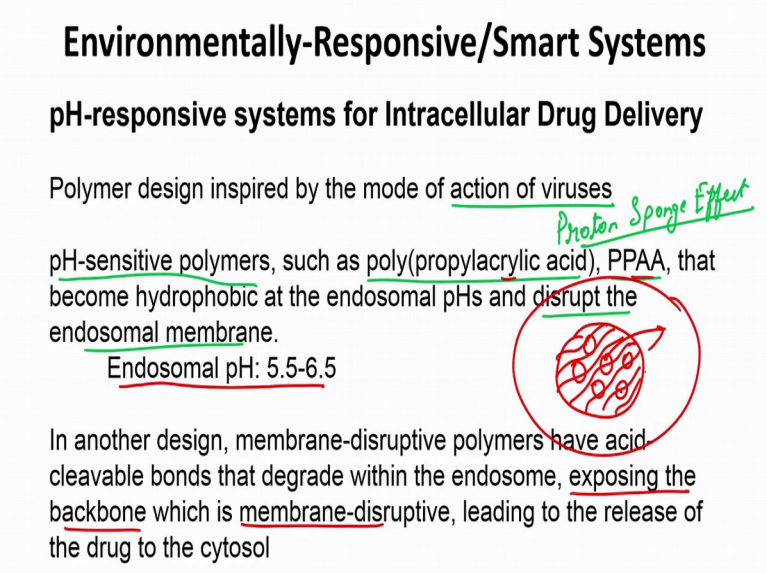

So, let us start with the pH responsive systems for intracellular drug delivery system. So, as I briefly mentioned earlier already that polyacrylic acid which is a carboxyl rich polymer can be used to act as a responsive system because at low pH it will be insoluble at high pH it will become soluble. So, let us see how it is being used here.

So, this is a system that has been designed through a virus inspiration, and in this case, we are talking about proton sponge effect. This is also something we have discussed in the previous classes. So, this is basically a pH sensitive polymer which means that it can absorb a lot of proton and it can then disrupt the membrane. In a similar example here, what we are talking about is these acid containing groups they will become hydrophobic and endosomal pH.

So, now we are not talking about the proton sponge effect, but what we are saying is there are other polymers that instead of utilizing proton sponge effect which was absorbing protons, we will have polymers that will become extremely hydrophobic at that pH because again they are insoluble, they are not ionic anymore or could be some other reason as well and so, because now they are fairly hydrophobic they will now start to interact with the endosomal membrane. And why will they do that?

So, let us say if this is an endosome containing your particle, this particle initially was fairly hydrophilic and there was because, we needed it to be hydrophilic because we want to maybe circle have it circulate into your circulatory system into a blood system.

So, it cannot be very hydrophobic because otherwise it will try to precipitate out. So, it was are earlier hydrophilic. So, at pH 7 this is hydrophilic, but once it goes to pH of let us say 5, because of these chains which may have a different pKa for their acid groups, it has now become completely neutral and the polymers themselves are fairly hydrophobic. So, because now there is no more ionic charge is no longer hydrophilic. So, this has now converted to hydrophobic.

Now, that this is hydrophobic and there is obviously, aqueous environment in the surrounding endosomal media. What this particle will try to do is will try to interact with the hydrophobic domains and so, it will go and start to interact with the membrane because remember membrane is nothing, but something like this, where you have a hydrophilic component and a hydrophobic tail. So, it will now try to interact with the hydrophobic tail because it does not really want to interact with anything, in that process it is going to cause disruption of this well-organized membrane causing the endosomal escape.

So, something a trigger of let us say pH 5.5 to 6.5 will be good for this to happen because this is an endosomal pH. If we design something which goes to lower pH let us say pH of 2, then we are under the risk that the drug may already be destroyed that is being encapsulated. So, it is important to then design polymers that show this property at a higher pH, but obviously below 7.

So, in another design the membrane disruptive polymers have acid cleavable bonds. So, you may not really want to disrupt the endosome itself, but you can have basically these polymers that are forming these particles to be cleavable at low acid. So, there may be rate of hydrolysis goes up exponentially as the pH decreases. What will happen then? It will cause the drug to come out. So, all of this drug which was initially entrapped, starts released very quickly once it goes to endosome as the pH drops a little bit.

Now, the drug that is being released is also released with some molecules that are membrane disruptive or maybe the backbone of the polymer itself is membrane disruptive. So, you can design various systems like that. But, what that will cause is then the membrane of the endosome which was encapsulating this will start to break apart because of these molecules being released and then causing the release of the drug in the cytosol.

So, these are some of the ways you can innovate with these systems and the possibilities are essentially limitless, you can do all kinds of innovation to tailor your system to suit various needs.

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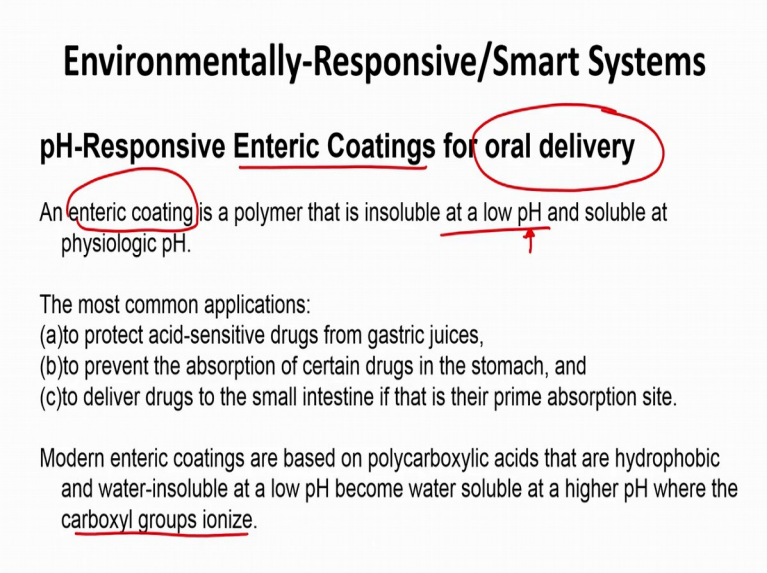

So, as I said, enteric coating we have already discussed I am not going to spend too much time on it now, but these are coatings with a polymer that are insoluble at low pH, but becomes soluble at physiological pH. So, this is usually used for oral delivery that is because when we take any tablet orally or when you take anything orally it first goes to stomach which is fairly a harsh environment and low pH and we want our drug to be protected in that environment. And then as the tablet moves down and goes to the intestine, the pH increases and at that point these coatings will become soluble, they will just solubilize and go away thereby releasing the drug which was inside these coatings.

So, again some of the common applications are to prevent your sensitive drugs from gastric juices, to prevent absorption of certain drugs in the stomach. So, maybe you want absorption to happen further downstream of the stomach, and then to deliver it to the small intestine which is where anyways the most of the absorption happens.

Modern enteric coatings are based on polycarboxylic as I was saying, that are hydrophobic and water insoluble, but as soon as their carboxyl groups ionized at a slightly higher pH they become soluble and then they can dissolve away.

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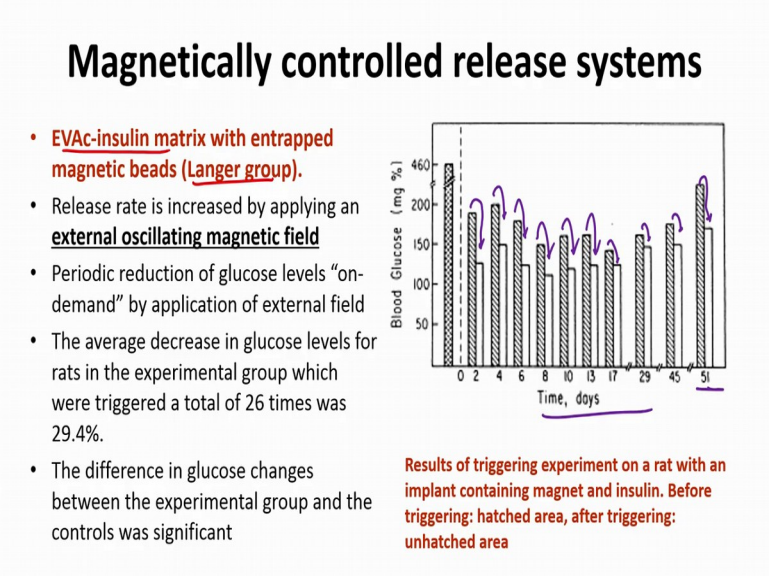

Then you have magnetically control systems. So, this was for the pH again as I said there are several other examples you guys can read further literature if needed, lots and lots of papers are published making different kinds of polymers that are pH responsive. Again this course is just giving you some brief overview. We are not going to completely exhaust all the systems that are out there. And again, if we cannot really do that because pretty much every month there is some new papers publishing new study about some other innovative systems.

So, this gives you a brief overview now and magnetically controlled release systems. So, one of the example that was developed by a group, Robert Langer in US, this is an EVAc insulin matrix system and that entrap magnetic beads in it. So, what the magnetic beads? These are small particles that are magnetic nature may be made of iron oxide, and other similar magnetic material. So, what this showed is that the release rate is increased by applying an external oscillating magnetic field.

So, let us say if you have a particle system, this is encapsulating these magnetic beads, maybe iron oxide particles and also some drug. So, let us say it present drug with another color. Let us say this carries a peptide which is being shown with the magenta color or purple color here. So, if in a standard system this peptide is coming out at a certain rate because it is either diffusing or maybe the particle itself is degrading. What happens now is that you apply an oscillating magnetic field, these green dots will start to move with

the magnetic field and it start to oscillate. Because of that you are causing a lot of movement, so you are increasing first of all the diffusion the pore size will get expanded you are actually sometimes even disrupting the pores there will cause a release to go higher and that is what was the concept that will used in this particular example.

So, what they were proposing this as is to use it as a periodic reduction of glucose levels on demand. So, let us say if I just ate food and there is a certain requirement for insulin to be secreted which is now encapsulated in this particular polymer matrix. So, in that case what I can do is I can then just apply the magnetic field in the area where these particles or these systems are implanted and because of that there will be sudden release of quite a lot of insulin, which will then cause the blood glucose level to go down. So, this is where this is their data showing that.

So, as you can see you have you have blood glucose level here at time 0, of course you have a certain blood glucose level which is diabetic in nature on a rat experiment. And then you put on an implant containing these magnet beads and insulin and this is before triggering, so right before dragging all the hatched area is what you get the insulin level or where the blood glucose level is actually before triggering, but as you trigger more and more insulin gets released and because of that what you see is you see a drop in the blood glucose level. So that means, that insulin is releasing in higher amount when you are putting the magnetic field and not only that its it is actually functional and this is able to reduce the blood glucose even for a timeframe of up to almost 2 months.

So, the average decrease in glucose levels for the rats in experimental group which were triggered a total of 26 times, this was done 26 times, and there was about 30 percent reduction every time this was done. And the difference in glucose changes between the experimental group and the control was significant. So, all of this was actually significant and so, they were able to show that such magnetically triggered systems can be then externally controlled and depending on when you need it, so, maybe right after you have it your food, you can just have this magnetic system get triggered for some time, and then you can then go back to your normal lifestyle.

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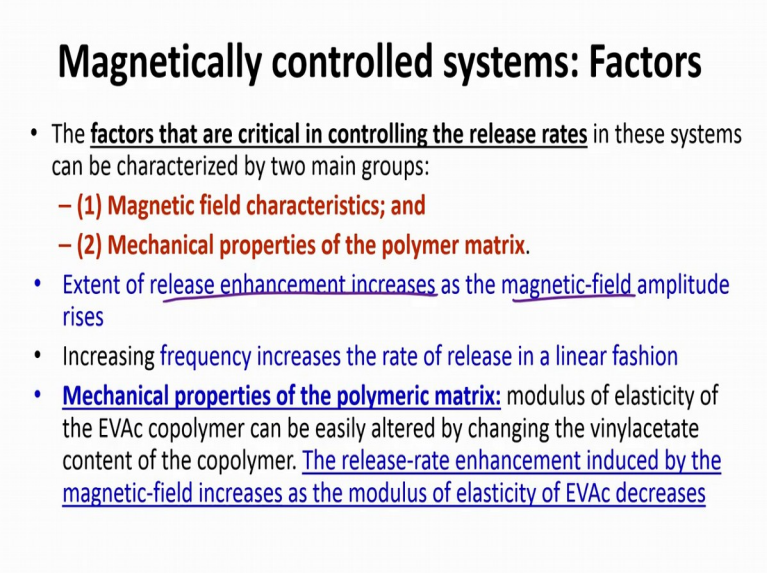

So, what are the different factors which control this magnetic system? So, the factors that are responsible can be basically categorized into two main groups. One is the magnetic field characteristic, so what type of magnetic field we are applying, how long and all that and another is the mechanical property with the polymer matrix. So, obviously as I said that this is actually physically disrupting the polymer matrix and by movement and all. So, mechanical properties of the polymer matrix will also play an important role.

So, as you increase the magnetic field the release is enhanced and then this is fairly obvious the more magnetic field you are applying, the more energy and imparting to the system and this is going to cause more release of your drug from the particular system.

So, if you do more frequencies. So, as you as you continue to do it multiple times you are increasing the release rate in a linear fashion and then the mechanical properties the polymer matrix is also important, the modulus of elasticity can be easily altered for some of these polymers by changing their ratios of various copolymers, that are being used or just the ratio that was initially used to form these matrices and the release rate enhancement will increase as the modulus of elasticity decreases. So, the softer it is the more the release will be, which is again fairly obvious, the same amount of energy you are giving to a soft system, it is going to disrupt it in much higher amount and then say a hard system.

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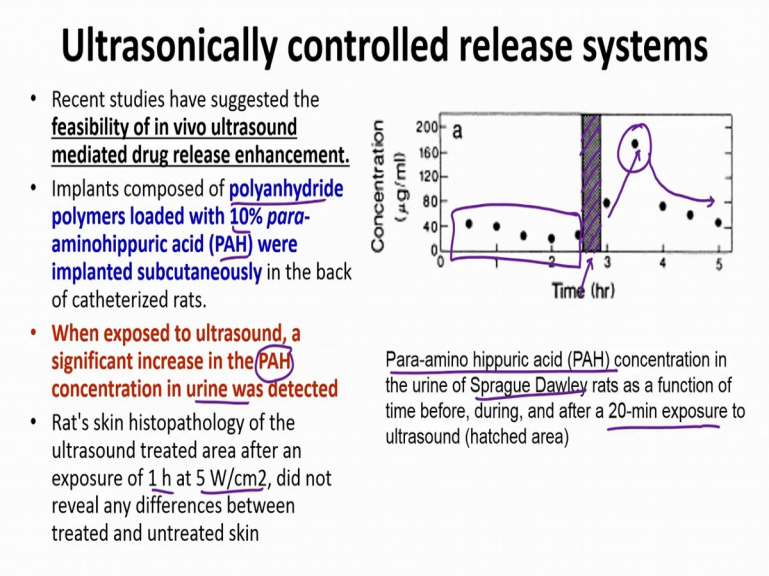

So, another topic we will talk about is ultrasonically control release system. And again, this is very similar concept to the magnetic system. You are giving some external stimuli that is giving some energy to your device and that device once it receives that energy, is responding to that energy, either in the previous case as we seen by disrupting the polymer matrix and in this case as we will see.

So, again, one important thing with the ultrasound is an ultrasound is already used clinically. So, it is very commonly used people will undergo ultrasound procedure for various kinds of diseases, this is well prescribed by doctors. So, it is known to be fairly safe. And that is what, this is being used by the field to see if we can use this ultrasound to mediate drug release enhancement.

And in this particular example that I will give you, we are talking about polyanhydride polymers that are loaded with 10 percent PAH, and these were implanted subcutaneously in the back of a rat. And then when these were exposed to the ultrasound you had increased amount of this PAH drug being detected in the urines so that means, that the system was releasing more PAH and then that PAH was these eventually cleared away by the urine. And so, here is the data on that. So, you have, again as I said, here is your drug PAH and this is the concentration of the drug in a Sprague Dawley rats as a function of time.

So, this is basically what you were seeing before you had given any ultrasound. Then you gave the ultrasound energy at the location where the implant was put in these rats and then you measured the amount of PAH being excreted out through the urine. And what do you find? This is a 20 minute exposure of the ultrasound. And what do you find is that following that after a few hours, you start seeing after, in fact, within an hour you start seeing very high concentration of PAH being present in the system as well as being released from the urine and eventually it goes down because since you have stopped giving the ultrasound, the energy is no longer there, so it goes back to the basal rate, what it was earlier.

And then they have been rat skin histopathology to see if that has caused any kind of damage. So, they did an exposure of about 1 hour for 5 Watt per centimeter square of the skin and then find that there does not seem does not appear to be any differences in terms of how damaged the skin has got because of this treatment. So, this treatment is fairly tolerable by the animal.

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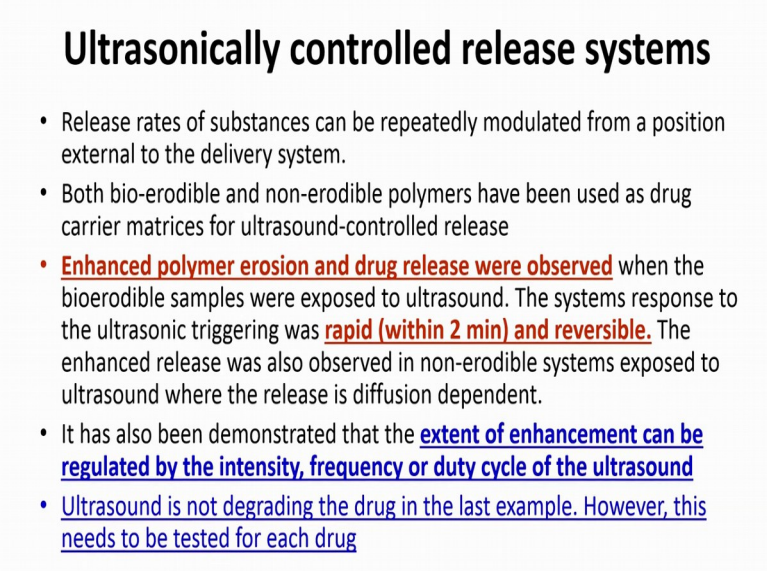

So, again if we talk about what this system entails the release rate of the substance can be repeatedly modulated again because you can switch on and off the ultrasound, depending on your convenience. So, you have an external control over your release.

You can use it with both bioerodible and non-bioerodible polymers with ultrasonic controlled system. If you are using bioerodible polymers then there will obviously, if I

then start plotting the release rate, maybe there is some release that is happening because the polymer matrix is being eroded and then now if I give ultrasound what will happen immediately some of it will come out further because this enhance diffusion. And then once I stop by ultrasound will go back to being eroding and then this can be done on multiple cycles.

So, I hope you can then appreciate how you can then carry it forward for several repeated cycles of this. And obviously, this can be on a period of minutes, this can be on a period of hours; this can be in a period of days and weeks. So, depending on what do you want in terms of your application, you can do this. And again, here also this can, depending on how much drug you are loading, this can go on forever or this could be a non-erodible polymer matrix in that case the drug will only release when you will have some ultrasound. So, you will see something like this. So, just depends on what the application is if you want some basal level you may want to use the bioerodible polymer, but if you want a complete control of when it is releasing you may want to use a non-erodible polymer for this setting.

Obviously, if you are going to disrupt a erodible polymer what will happen is that the water will also be able to penetrate quite quickly as well and so, you will cause some enhanced polymer erosion as well. So, that is how you can tune the system also, depending on what do you want to achieve from the system.

It has also been demonstrated that the extent of the enhancement can be regulated by the intensity. So, again just like your magnetic control system if you increase the intensity of the ultrasound, if you increase the frequency, if you increase the duty cycle of this how often and how longer you are giving this, all of this will modulate your release rate. So, it is fairly well controlled system that you have at your hand because depending on the application you can then, let us say if you want to release more drug you can then give more intensity of ultrasound if you want to do less drug you can give less intensity. So, all of that is controllable.

In this case obviously, there is a concern that ultrasound itself may degrade the drug because it is giving some energy, however in the last case nothing of that sort was observed, but this is another thing that you must consider that whether your drug is compatible to a repeated ultrasound exposure or not. So, some drug may not be very

friendly for this method because let us say with like it is a protein that is prone to denaturation with small energies and small perturbation in the system and then these ultrasound may actually deactivate that protein. So, this is something that you need to consider while you are designing a system.

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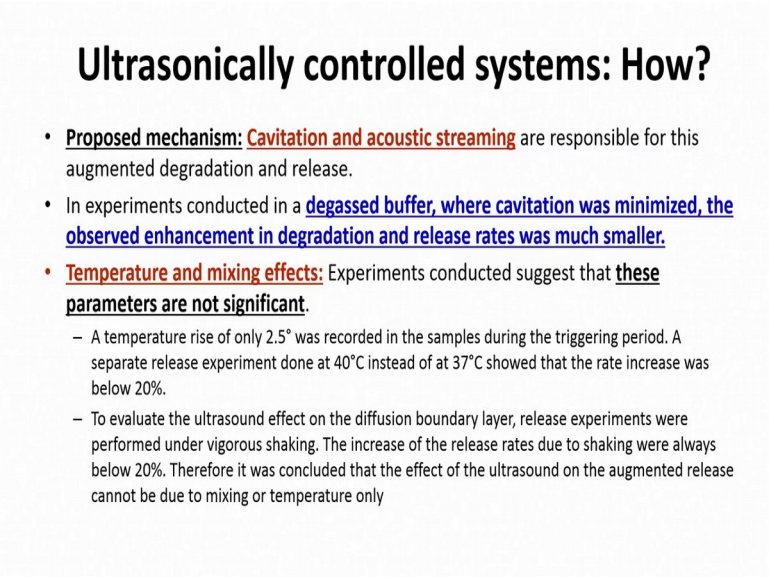

So, how does this happen? So, the proposed mechanism is obviously, cavitation in acoustic streaming and which are responsible for degradation and release. So, if you do an experiment in a degassed buffer, so you have taken a buffer which is completely degassed. So, now, you have minimized the cavitation in that scenario and you find that the release rate and the degradation is much smaller. So, that is how you can conclude that cavitation is one of the major player and that causes the release rate to increase.

And then obviously, there are some temperature and mixing effects that can also happen, but then when the experiments were conducted, they found that the temperature increase was not very significant, the temperature rose only about 2.5 degrees during the triggering period. And then, it was shown that there is not much change in the release rate at different temperatures. And similarly, the ultrasound effect on diffusion boundary layer was also seen in the release experiments performed with vigorous shaking and again it was found that it is not very significant. So, it is basically cavitation and acoustic streaming that is causing the system to work.

So, we will stop here and we will continue a discussion further in future classes.

Thank you.