Drug Delivery Principles and Engineering
Prof. Rachit Agarwal
Department of BioSystems Science and Engineering
Indian Institute of Science, Bengaluru

Lecture – 13
Math Exercise

Hello, everyone. Welcome to another lecture for Drug Delivery Engineering and Principles. We have been discussing quite a lot of mathematics and quite a lot of how to compute different things for determining release date for determining how the drugs have being distributed in the body. So, I thought in today's class we will just give you a little bit of exercise and we can walk through some of the questions and solutions to those.

So, that will help you in terms of first of all relating as to how these are being used in actual clinics and how these problems can be solved and then it will again help you in your exams and assignments because some of these problems will be similar to what you may expect in your exam ok. So, to start off, let us do sort of recap of whatever we can do. I have planned out about 6 or 7 exercises in this lecture. So, let us get into that.

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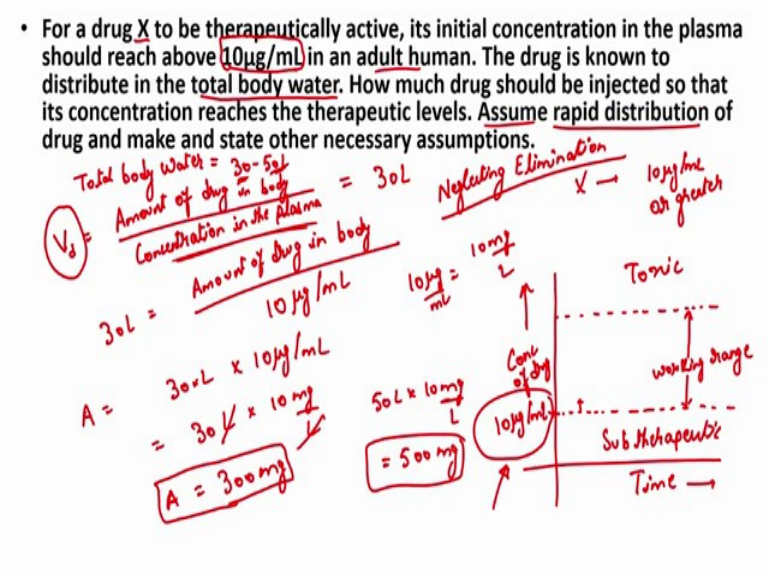

So, here is a question the question is for a drug X. So, could be any drug, could be any of the drug, may be any drug that may relieve hypertension, that may relieve diabetes, it

could be anything. For a drug X to with therapeutically active, its initial concentration in the plasma should be above 10 microgram per mL. And that is in an adult human.

So, basically what we are saying if we have a drug X and for it to be therapeutically active we need to gets it is concentration to be 10 microgram per mL or greater. Now, this is again very clear, well I will also explain a little bit as we go long. So, we know that for every drug there is this toxic level. So, this is if I say concentration of the drug and then there is some sub therapeutic level.

So, this is toxic, this is sub therapeutic and let us say this is time. So, for any drug we can define these two parameters; obviously, if you keep giving the drug and it reaches a certain amount it may start becoming toxic to the body and below certain amount it would not even do anything. So, it will be as if there is no drug and this is the region you want to work with, basically the working range.

Now, for this particular drug X, we are saying that this value is 10 microgram per mL. Obviously, the upper limit is not given in the question, so we will assume that somehow we need to get the concentration above this particular value. So, now, this drug is also known to distribute in the total body water. So, now, that comes to our discussion on the Vd which is the volume of distribution and it is saying that this drug distributes throughout the body water.

So, what kind of drug this will be? This will be fairly hydrophilic drug. And, so, the question is how much drug should be injected, so, that its concentration reaches the therapeutic levels? The question assumes that the drug is rapidly distributed and may consider other necessary assumptions.

So, obviously, if we talk about real clinical scenario we need a lot more information which is not given in this question because technically we should know what is the elimination rate right because let us say injected drug, but even before it goes to the 10 microgram per mL, it starts eliminating also, so we need that rate also. So, that is why one of the assumption that they are saying is it is a rapid drug distribution. So, we can assume instantaneous distribution for this for this problem and then of course, there are a lot of other assumptions we have to make as to what is the weight of the human, what is the total body water present. So, all of that assumption we will make as we continue in this.

So, from our discussion in the class let us say for an adult human, the total body water is about 30 to 50 liters that is what we are discuss right. So, let us take an example of 30 liter and then we know what Vd is: the volume of distribution is amount of the drug in the body. So, basically

(Amount of drug injected)/(Concentration in the plasma)

So, we know that if Vd is very high; that means that the concentration in the plasma is fairly low which basically would suggest that it is a lipophilic drug, but in this case it has been given that the Vd is actually the total body water. So, let us assume this to be 30 liter. Now, since we are saying that we want the therapeutic concentration to be 10 microgram per mL, the concentration in the plasma which is again a part of the body water, should also be 10 microgram per mL.

So, what we can then do is we can then just say that 30 liter is equal to the amount of the drug in the body which is the total amount that we are injecting, given it is an instantaneous distribution and we are neglecting any elimination, so let me state this. So, here we are neglecting elimination, at least for the time frame that we are talking about here. So, now, we go with this, we are saying that the

30 L= Amount of drug in body/ Concentration in the plasma

Concentration in the plasma in this case is 10 microgram per mL.

So, then the amount of drug in the body, that is basically what we are injecting is equal to, so let us say that is

A=30L x 10 µg/mL

So, let us just convert this mL to liter and microgram subsequently. So, if I say so,

10 µg/mL = 10 mg/L

All I have done is divide is multiplied both sides by thousand and then 1000 microgram is 1 mg and similarly 1000 mL is 1 liter.

So, then we can say that this is 30 liters multiplied by 10 mg per liter; liter-liter we can cancel. So, there will become 300 milligram. So, that will be the amount of drug that we

will have to inject and that will lead to the concentration of 10 microgram per mL; obviously, in a real scenario we will have to inject a lot more than this because there will be elimination as well and then we again want to be above this not at this and so, that is why it will be this. So, 300 milligram is the bare minimum that we will have to inject for the drug to be actually therapeutically active.

Obviously, we would have assumed the total body water will be 50 liter. This would have just turned into 50 liter multiplied by 10 mg per mL or 10 mg per liter giving us a value of 500 milligram. So, now, you can see how the doctors can then, if a patient comes in and the patient is tall and heavy then they will have to give a lot more drug, whereas let us say if it is still a kid or some person of that size. And, that is why the doses all the differ between women and the men because typically there is a difference in the weight also.

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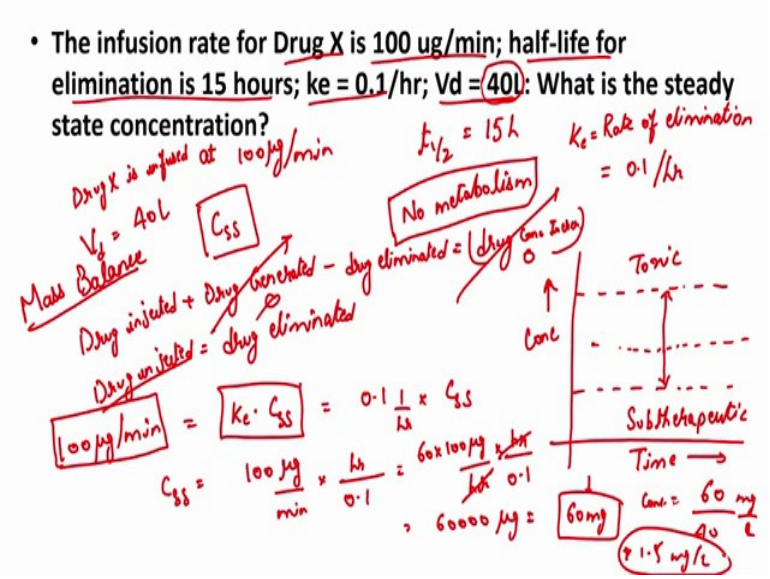

Here is another question. So, in this question again this is more on the first part of the talk, first part of you of the course we will be talking about pharmacokinetics. So, in this particular question what has been given, is a drug X has a infusion rate of about 100 microgram per minute. So, basically we are saying that drug X is infused at 100 microgram per minute. So, maybe it is an IV drip you have seen if you go to the hospitals, they will have this stand with a bottle and connected to your veins through a tube.

So, maybe it is something like that scenario and where they are allowing about 100 microgram of drug to go in per minutes. Now, what they do that may be the drip has a concentration then they are releasing maybe 0.1 mL per minute and that comes out to be 100 micrograms. So, something very achievable and then now they are talking about elimination here as well and they are saying the half life for the elimination is about 15 hours.

So, we know that t half is equal to 15 hour, then they have given the rate of elimination also. So, the ke which is the rate of elimination is equal to 0.1 per hour. So, and then the Vd is also given to be 40 liter. So, again and this Vd is fairly high which means that the drug must be hydrophilic and given a previous problem, it also appears that it is also distributing the total body water. And, so now they are asking what is the steady state concentration. So, let us say I write the steady state concentration as concentration at steady state. So, this is what we want to find.

Now, let us look at the scenario. So, we have a patient. The patient is being in continously given the drug by a drip, but we are saying that the drug is not going to be stable there forever and it also has some elimination rate, it also has some half life. So, then how much should I give? So, again if I draw that curve again. So, again this is the toxic level, this is the sub therapeutic level, we have concentration versus let us say time. Now, in the previous example what we looked at how we can get to this particular range. Now, what now we are trying to do is to see if we can maintain in this way.

So, let us say if we are here and we want to maintain it in such a way that it does not really go away from this particular range, then we have to continuously infuse it because this drug is degrading and if we now continuously give the drug then we will remain in this range. So, in this particular problem since we are saying that the drug is also getting eliminated, we have to balance for that. However, the metabolism of the drug is not given. So, in this case we will assume that there is no metabolism or even if there is metabolism it does not really change the activity of the drug.

So, maybe the metabolites are also active or maybe there is no metabolism which is again not a physiological case. There will be some metabolism as well, but for now let us assume that there is no metabolism it is only infusion and elimination. So, now, that is

the case then at steady state since the drug cannot be generated in the body, what we will say is, let me do a mass balance here.

Drug Injected + Drug Generated - Drug Eliminated = Increase in Drug amount

Now, we are saying a steady state, so, drug added is 0, when I said drug added, it is like the increase in the drug concentration , but since it is steady state, so, let me just actually say is equal to the drug concentration increase. So, this is 0 because it is a steady state we are saying the drug cannot be generated so, this is 0. So, then what we have is basically drug injected is equal to the drug eliminated. This is nothing, but a mass balance.

Now, let us look at each of these, so we know that the drug injected is 100 microgram per minute and what about the and drug that is eliminated? So, let us assume, well we do not really need to assume because the ke is given to us. So, what is ke? ke is the rate of elimination. So, if I then equate it to the ke multiplied by the concentration of the drug at that time. So, let us say the Css because we are saying that is the steady state concentration, so that is not changing. So, this should then be equal because this is the amount of drug that is getting eliminated per unit time and this is the amount of drug that is getting injected per unit time.

So, if now that is the case, then it becomes simple. So, all I have to do is ke we know is 0.1 per hour multiplied by the Css and that should give me the steady state concentration. So, then Css will basically become 100 microgram per minute multiplied by, correct. Now, I have to match this unit, so to do that what I can do is I can convert this. So, I can multiply by a 60, I can convert this to hour so that I can cancel this, so this will basically become 60 multiplied by 100.

So, that is now microgram divided by hour. This then gets multiplied by hour divided by 0.1. So, the hour-hour gets cancelled, so this essentially will become 60000 microgram, which you can convert to milligram. So, that will give you, that will give you about 60 milligram.

So, now, this is the total drug that is going to be present in the body at steady state. Now, we know that the Vd is 40 liters. So, that means that this amount of drug will be distributed in this volume. So, then the concentration will be nothing, but 60 by 40

milligram by liter. So, that will basically give us 1.5 mg per liter or even convert it to whatever unit may be desired ok.

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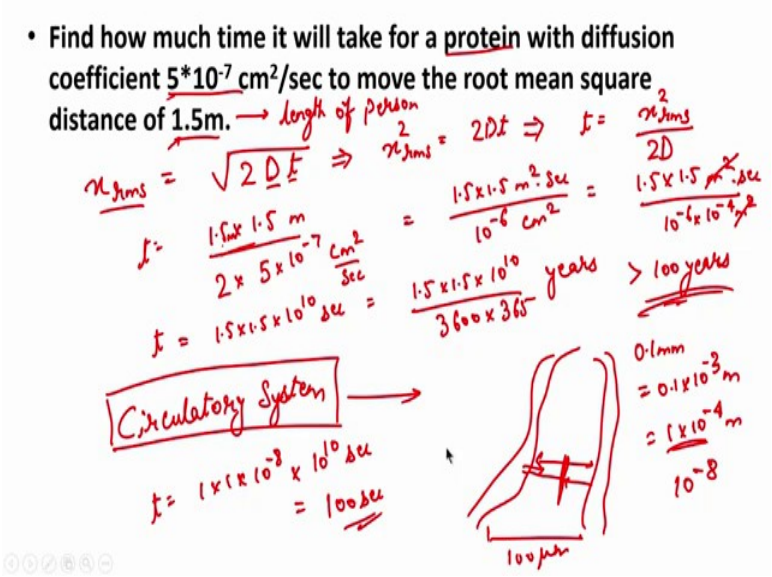

So, let us look at another question now. So, now, we are moving towards the diffusion part of the course and the question is how much time it will take for a protein with a diffusion coefficient of 5 x 10 to the power minus 7 centimeter square per second to move the root mean square distance of 1.5 meter. So, now, what is it 1.5 meter? That you can consider is let us say a length of a person, we are anywhere between 1.5 to 2.1 meters and depending on how tall or short we are.

So, basically the question is asking how long will it take if I have a protein let us say in my brain for it to reach my feet, just my diffusion. So, this is a very simple question in this case because we know that the root means square

$Xrms = (2Dt)^{0.5}$

So, now, what we know? We know the Xrms, we know the diffusion coefficient for that particular drug in that media or that particular protein in that media and then we want to find out how much time it will take. So, let us do this.

So, this will basically become if I square both sides.

$(Xrms)^2 = 2Dt$

$t = (Xrms)^2/2D$

So, I just want to point out that this diffusion coefficient which is written here is actually fairly physiological, this is how the typical protein diffusion coefficient is what you will find in the literature and again the distance that is given here 1.5 meter is again very physiological as well because that is what at least for human case scenario you will find this being the requirement for the proteins to go throughout the body.

So, now, if I solve this, so we will get

$t = (1.5\ m \times 1.5\ m) / (2 \times 5 \times 10^{-7}\ cm^2/s)$

So, this will then become

$t = 1.5 \times 1.5 \times 10^{10}$ seconds

So, now, this is quite a lot of time right I mean if I convert this to let us say hours and I will basically do. So, this will be hours. If I now actually want to convert this into years it is going to become this many years it will take for this protein to diffuse. Now, even with all this if I see here now, so we are talking about 1, 2, 3, 4, 5 ,6. So, I am still talking about 100s or 1000s of years, so almost about 500 years or something. So, I am not going go ahead and solve this right now, but we are talking about this is going to be greater than 100s of years.

So, now, you can imagine if we are saying that a protein if it is moving purely by diffusion from our head to all the way down to our feet is going to take about more than 100 years then we have a big problem right because eventually all these proteins, all these biomolecules need to move freely around. So, what are the different things that we can change about that? Obviously, that is not true right because we know that that is not true, we have insulin secreted in one part of the organ, but immediately goes to everywhere else. We eat food, even though it gets absorbed through our gut it goes to all the parts of the body.

So, that is where the circulatory system comes in, because if we do not have the circulatory system and if we require only diffusion then we are taking years for that. In fact, this is much more than the lifespan of the human. So, that is not physiologically feasible, so maybe that is where the evolutions of the circulatory system started to solve

this diffusion problem, this transport problem that we had. So, the only way otherwise is you change the diffusion coefficient which of course, you cannot. Some molecules do you have higher diffusion, but even if you have a 10 times higher diffusion even then we are talking about years.

So, the circulating system is obviously, very fast, our heart beats pretty much 100 times a minute and that ensures that everything is well distributed to all the parts even though between the two blood vessels there might be gaps. So, let us say here there are two blood vessels and this region will still require diffusion of the protein from here to here, first of all some kind of transport receptor to take this protein and shuttle it across, if it is not really diffusing through the blood membrane. And then once it comes out here it still needs to diffuse in to reach the site of action and, but then this distance is then reduced to about 50 microns, or 100 microns let us say.

So, we are talking about 100s of microns here and now if I substitute that, it changes a whole lot because 1 micron is nothing or let us say we go with this. So,

$100\ \mu m = 0.1mm = 0.1 \times 10^{-3}\ m = 10^{-4}\ m$

So, now, if I square this which is being done here you will find that this is going to become 10^{-8} on the numerator and that will basically meaning, so, if I now substitute here for this, then we are talking about

$t = 1 \times 1 \times 10^{-8}$

So, this is for 1 instead of 1.5 meter here and then all the numerator will convert it into the power 10 seconds which is going to give us about 100 seconds. So, because of this circulatory system, we are able to reduce the time of diffusion from 100s of years to 100s of seconds, which is much more relevant in our case, that is why the circulatory system helped us in quite a lot to carry out normal processes ok.

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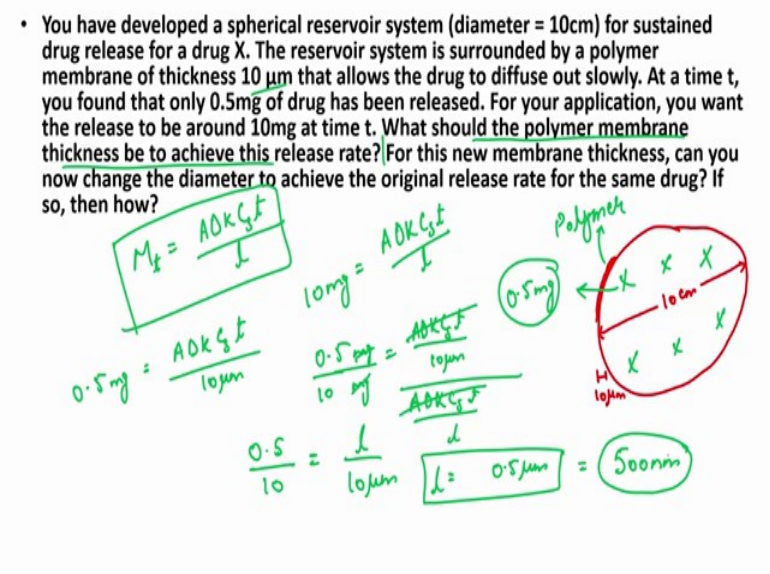

So, let us look at the fourth example now. So, let us see what this example is, this is more on the reservoir system now. So, we are moving further as towards the middle of the course and let us see what they are saying. So, they are saying we have developed a spherical reservoir with a diameter of about 10 centimeter for a sustained release of the drug X. So, obviously, this is a reservoir, maybe there is some thickness to this membrane which is also given to be about 10 micron and all of this is filled with, let me use another color. So, all of this is filled with the drug X and this is of course, a polymeric membrane and this reservoir system allows this drug X to diffuse in through this membrane to come out and this was designed, a certain amount of drug was loaded into this. However, at any time t, we found that only 0.5 milligram of drug is coming out. So, but for our application, we want that drug to be about 10 milligram at that particular time t. So, we are almost 20 times lower then what we are supposed to do.

So, the question is then what should be the polymer membrane thickness be to achieve this release rate? So, this is the first part of the question and then another part that will tackle sequentially. So, we know that for the reservoir system the amount of drug released Mt is nothing, but the area, the diffusion coefficient, the partition coefficient of the drug, the concentration of the drug in the membrane multiplied by time t and the total thickness of the membrane. So, this we know for a reservoir system.

So, now, in this case we know, if you substitute this, we are saying that 0.5 milligram. So, we do not know lot of these values, but that's ok. We will let them be. At time t and we know this thickness to be 10 micron. And, now we are saying what should be this thickness, so that this value becomes 10 milligram instead of 0.5 milligram. So, again these values for the same device will remain the same, including the time since we are saying in the same time , but what will change is this value which will let us say we say is l, the new thickness.

So, what we can do simply is just divide these two equations.

0.5/10 = $ADKC_s t/10$ μm on this side and then for the 10 the other question is $ADKC_s t/l$. So, obviously, these two get cancelled and what we will have is

0.5/10 = l/10 micron. So, this can l can go on the other side, so we will have a this thickness to be 0.5 micron which means that if we now decrease the thickness from 10 micron to 0.5 micron, we will be able to achieve that. So, this is nothing, but a 500 nanometer polymer thickness layer.

So, let us see what the next part of the question is. For this new membrane thickness can you now change the diameter to achieve original release rate. So, now, it is saying that we do not want to change the thickness anymore, the thickness will fix at 500 nanometer, this new thickness, but what should be then the diameter of the device to be able to change this. So, then it is fairly straight forward again, so we will apply the same equation. So, let us remove this.

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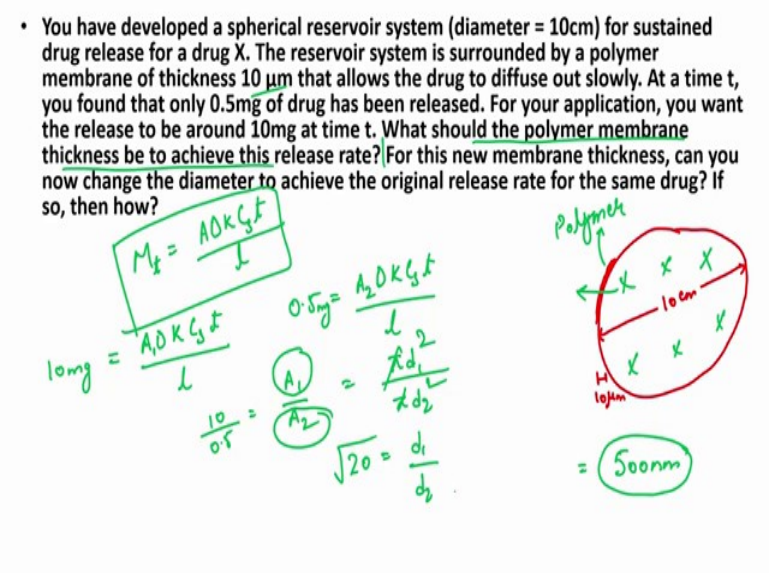

So, now, the values that are given to us is this that, 10 milligram which is the released amount is, let us say now because we are changing the diameter the area will change. So, I will define them as A1 and A2 then it will be DKC_st/l;

l in this case will be 500 nanometer, so I do not need to change that, but what we want is in another case you want the original release rate. So, another equation in the new device will be

$0.5\ mg = A_2DKC_st/l$

So, again we can do the same thing we can divide them again. So, let us say

$10/0.5 = A_1/A_2$ when where A_1 is the current area, A_2 is the new, so we can then expand them as well. So, we know that area for a sphere

$Area = 4\pi r^2 = \pi d^2$

$\pi d_1^2/\pi d_2^2 = 20$

$20 = d_1^2/d_2^2$

So, now, what you can do is you can then solve for this and get the ratio of these two. So, if I want a ratio I can just do a square root on both sides, so square root here and then if I do a square root this is going to get removed. And now I can find that how I can change

the diameter, I can increase it by certain amount I can decrease by certain amount to get the original release rate.

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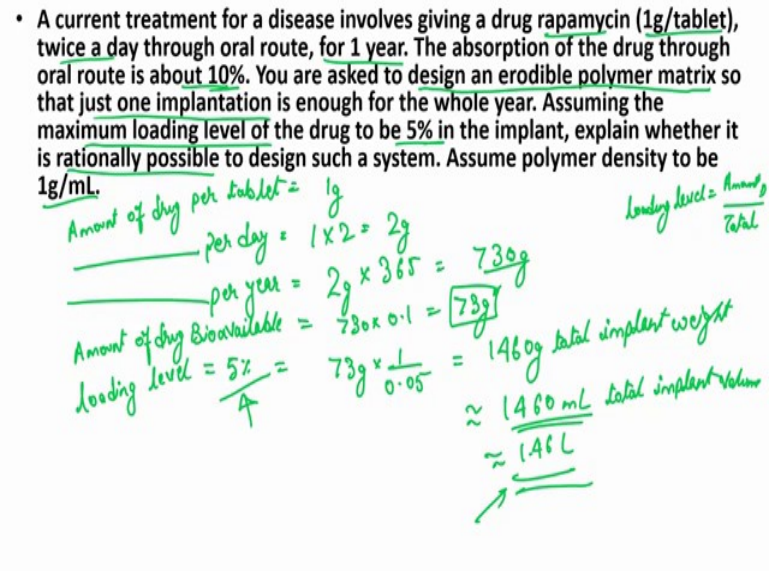

So, here is another question now, this is on the polymer matrix system. So, the question is a current treatment for the disease involves giving a drug; in this case the drug is mentioned as a rapamycin, for 1 gram tablet which is given twice a day through oral route and this particular treatment requires it to be given for about a year. So, quite a lot of drug that the patient has to take.

The absorption of the drug through the oral route is about 10 percent. So, for this particular drug, rapamycin, we are saying that it absorbs through the oral route at about 10 percent and now, you have been asked to design an erodible polymer matrix. So, your task is to design an erodible polymer matrix, so that the patient does not have to continue to take these tablets twice a day for 1 year, which is very patient non compliant, it might be easier to just do one implantation and that we able to release the drug for the whole year, so that is what you want. So, you want a polymer matrix which erodible and once you implant it, it should last for the whole year with the same amount of drug being delivered.

So, this is the question that you have in hand, you know that whatever polymer you may use for this particular drug, you may be able to achieve a maximum loading level of about 5 percent in your implant. So, remember the loading level is basically amount of

drug or I should say amount drug by the total amount of the implant. So, this I am saying is 5 percent.

So, even before you go into design insensate system you want to see this is even feasible. So, we want to see if it is rationally feasible to design such a system and you can assume whatever polymer you are using, its density is 1 gram per mL ok. So, now, given all that you are saying if it is feasible, so let us see what we can do. So, we know that the amount of drug that is being given, so amount of drug per tablet is 1 gram. So, and then this tablet is taking twice a day, so amount of drug per day is 1 multiplied by 2 which is 2 grams that is being taken.

Now, this is being taken for one year, so amount of drug per year and obviously, we are only talking about one year is 2 gram and then 365 days. So, this is the amount of drug that is being given. So, this will basically become 730, so we need to give 730 gram of drug for full 1 year. Now, but obviously, this is the amount that we are giving, but the amount that is getting observed is only 10 percent of that because we are saying that through oral route, we only get 10 percent into the system.

So, amount of drug which is bioavailable which is bioavailable for that whole duration is about 730 multiplied, by since it is 10 percent, so 0.1 which will give us 73 gram . So, now, we are saying that if we are implanting something and since we are going to implant this in the body everything, once the polymer degrades, will come out and remain in the body. So, we want to somehow make a device which has 73 gram of the drug.

So, now, having done that we know that the loading level. So, maximum loading level we can achieve is 5 percent which means that if I want 5 percent of the drug, then I need to have rest as polymer. So, then what is the total amount of implant there we need to put in?

73 g x 0.05

So, that will be the total implant device and this will, if you solve this will give about 1460 gram of the total implant weight.

Now, we are saying we can assume the polymer density to be about 1 gram per ml. So, this will basically mean 1460 mL total implant volume. Now, this is huge I mean this we are talking about again 1.46 liters which is huge. It is really through any doubt you would not get that much space to put in your implant. So, this is looking improbable to be able to design and this is assuming quite a lot of things that there is a 5 percent loading level which is actually fairly high.

So, in general we would we have to conclude that this is rationally not possible. However, if you can somehow increase the loading level and get it to let us say 80 percent, 90 percent, then we are saying that it is fairly feasible because 73 gram or let us say 73 mL is not such a big volume it is something that can be implanted, , but in this particular case the value comes out to be 1.46 liter which is not feasible.

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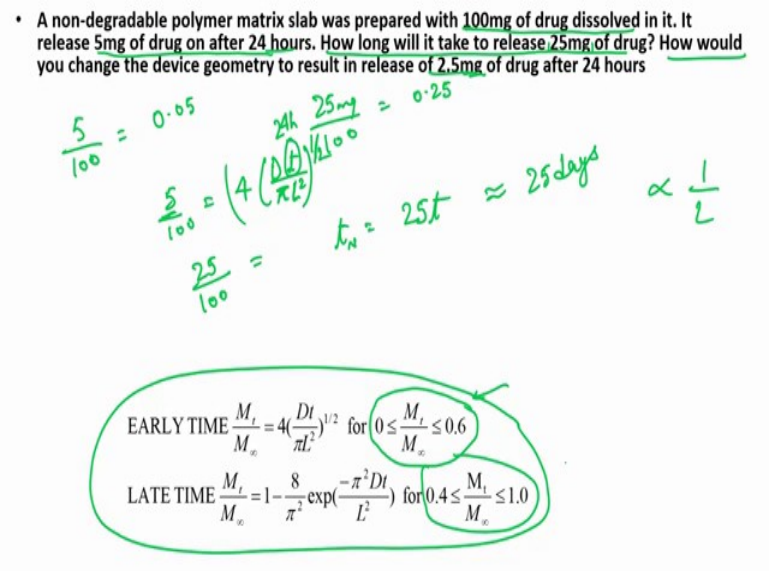

So, here is the last example. So, in this case we have been given that a non degradable polymer matrix slab was prepared with about 100 milligram of drug dissolved in it. So, and we are saying that it would release about 5 milligram of drug after 24 hours. So, the question is then how long will it take for the drug to be released, the total amount of 25 milligram? So, that is the first part of the question, so let us tackle that.

So, we already know that for a polymer matrix slab the equations are these for the early in the late time through our class. So, and this is of course, after approximation for early time and the late time where early time is anywhere between 0 to 60 percent of the drug

being released and late time could be anywhere between 40 to 100 percent of the drug being released. So, in this case we are saying the total drug that is loaded is about 100 milligram and what has released is only 5 milligram.

So, if I do this calculation so, this will be nothing, but

$5/100 = 0.05$

and for how long will it take for 25 milligram. We are still talking about

$25/100 = 0.25$

So, in both of these cases we can use the early time example. So, we will use the early time example. So, let us see.

$5/100 = 4(Dt/\pi L^2)^{0.5}$

Now, if this much is being released for this given length L; so, if you look at this equation the only thing that you can change in the device geometry is L, but we will come to that later. So, if this is the case then how much will it take? This is this is a time t let us say this time is 24 hours in this case.

So, to get to 25 milligram, so if I do

25/100. So, this time we will have to then increase by, this whole thing we will have to increase by 5 times because this is 5 times of this. So, then the t since which is in square root will have to increase 25 times. So, this will basically mean

$t_{new} = 25t$

So, since we are saying is 24 hours for 5 milligrams, it will take about 25 days for 25 milligram.

Now, we want to increase this release rate and we are saying the second part we are saying how would you change the device geometry to result in release of 2.5 milligram of the drug after 24 hours. So, we want to go back to 24 hours, but we are saying that we want to 2.5 milligram now. So, actually decrease the amount of the drug that is being able you want it to release it much longer time. So, we can still use the early time because it is still talking about much lower amount of drug than the total.

And, so if we do that then the only parameter we can change here is L which is nothing to device geometry. Everything else has nothing to do with the device geometry itself and if you look closely this is

$(L^2)^{0.5}$

so this is nothing, but it is a function of 1/L.

So, if I now want to decrease the release that is happening to 2.5 milligram from the original 5 milligram, I would have to then change the L subsequently, so that the whole thing becomes less by 2 times. So, the L would have to change accordingly. So, this is fairly easy to find out.

So, this is what I wanted to tell you in terms of exercise some just some basic knowledge about how to solve this, how to go about, how to apply this in actual practice and we I hope most of this is understood.

So, thank you.