Computer Aided Drug Design
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Lecture - 40
Pharmacokinetics/Pharmacodynamics

Hello everyone, welcome to the course on Computer aided drug design, we will continue on the topic of pharmacokinetics and pharmacodynamics okay.

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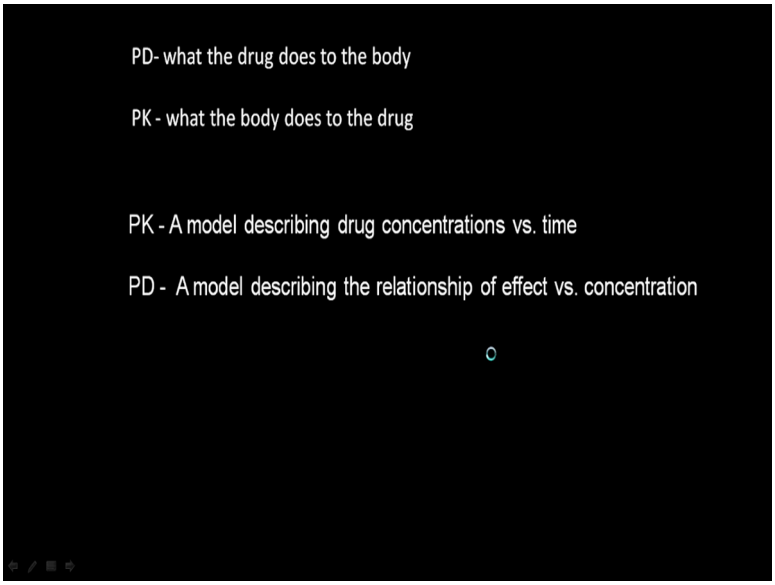

As I had introduced the topic yesterday, pharmacodynamics is what the drug does to the body, so if you have an infection the drug will go and try to kill bacteria, if somebody has a cancer the drug may go and kill the cancer cell. Pharmacokinetics is what the body does to the drug, because the body will start to metabolizing the drug, the body will start excreting the drug, tissue absorption, so many things can happen.

So pharmacokinetics is drug concentration reduces, drug gets eliminated, so both are very, very important okay. So pharmacokinetics model describing drug concentration versus time, pharmacodynamics model describing the relationship of effect versus concentration of the drug. So if you have different concentrations of drug what is the effect and so on actually okay.

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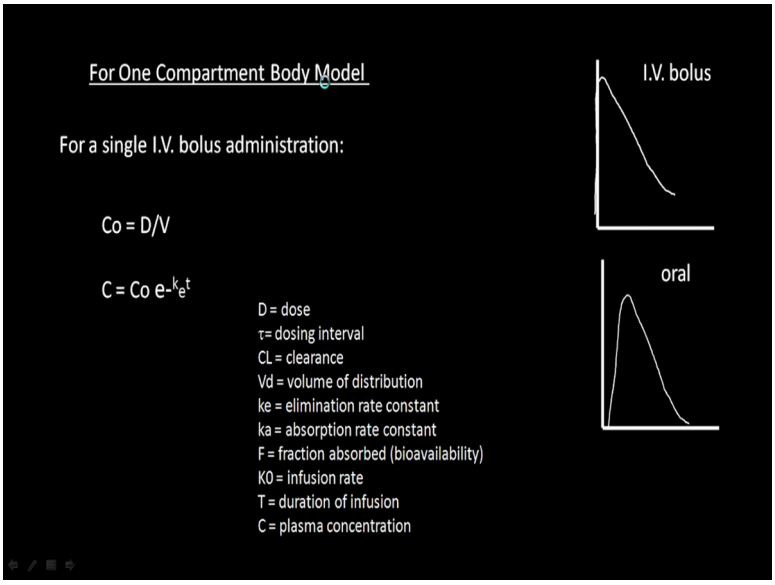

So yesterday we just talked a little bit on one compartment model okay, so we assume the entire body as one compartment, we do not differentiate between tissues and various organs into okay. And if it is a single IV intravenous bolus administration, we say bolus the whole drug is introduced in one shot, so we assume it within the 0 time the entire drug goes, it is like a short input okay.

We call it the Dirac delta function and so one, so in that case if it is an IV bolus initially it is the entire drug is inside in the plasma, and then it starts going down, because of elimination and metabolism, so we can assume it as the first order reaction sorry first order elimination C=C0 e-ke t, ke is the elimination okay, t is the time, C0 is this concentration here max. But whereas if it is a oral dosage drug will get absorbed slowly like that it goes and then reaches and comes down.

So this portion is still this equation exponentially decaying okay, whereas this portion we need something else to describe we will talk about this later. So if it is oral dose and you get this graph I said we draw line here and the slope will give you the ke/2.303 okay, and then if you extend this here where it touches the y-axis if you take antilog you get the C0. Of course remember this portion is logarithm of concentration, and this portion is time because of this know, so you need to have a logarithm here okay.

So this is one compartment model bolus administration, and as I said if it is oral then of course we need some one more extra term for the absorption through the gi okay.

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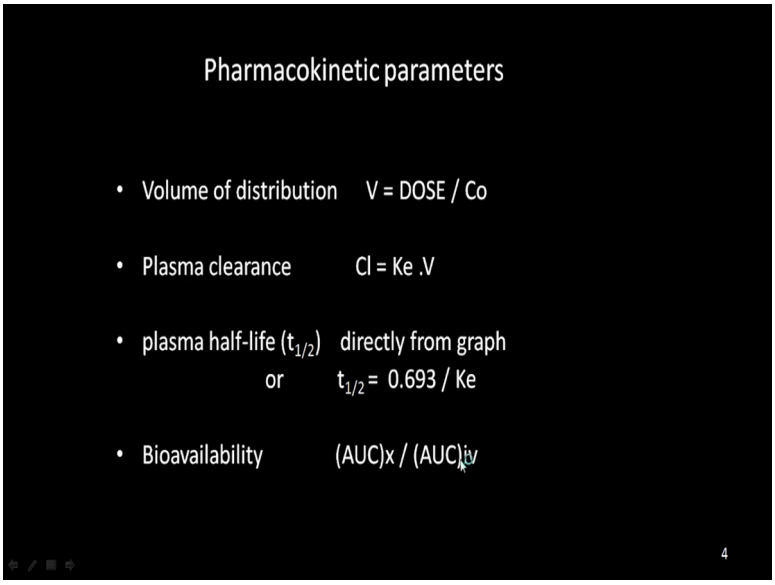

But before that let us look at it volume of distribution is given by V=dose/C0, plasma clearance is Ke elimination rate constant V, t 1/2=0.693/Ke okay. And then bioavailability is AUC if it is oral that is area under the curve if it is oral area under the curve is IV okay, because when you do IV the entire drug comes into the plasma region okay.

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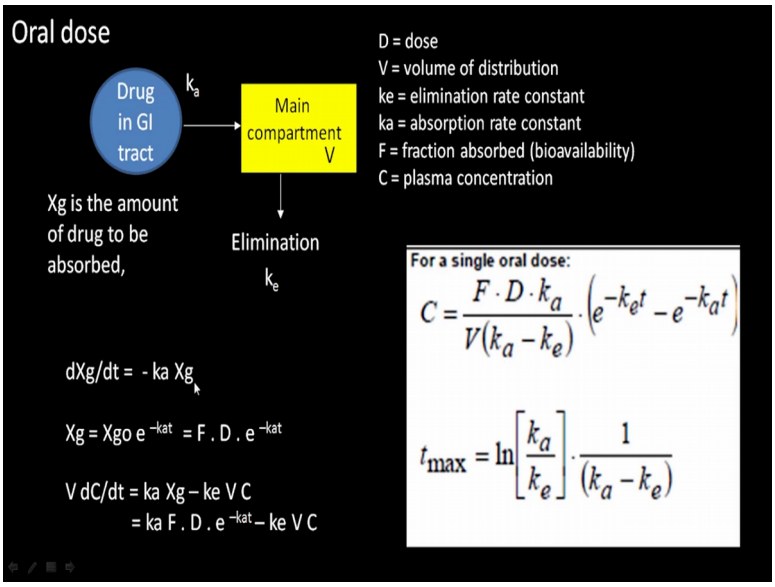

So oral dose if it is given as a oral dose, so we have a one compartment model the drug has to get absorbed so there will be an absorption rate constant coming here okay, and then of course it gets eliminated using ke, so this is just a single compartment, Xg is the amount of drug to be absorbed okay. So we can write model dXg/dt=-ka Xg okay, so Xg=Xg0 e-ka t okay k*time, so ka is the absorption rate constant okay, it starts going down because Xg0 it starts going down.

So this Xg0 can be written as F fraction absorbed that is the bioavailability*D, that is the dose e power-ke t okay, and then for the concentration of the drug inside if you assume it as C that is a plasma concentration, and that is given by V dC/dt=ka Xg that is coming in ke V C, ke is the elimination, and Xg we can substitute from this here, so we have V dC/dt like this this can be solved, it is not a big deal calculus okay, first order differential equations.

So you get a equation for C F*D*ka, that is the absorption rate constant/V volume of distribution ka-ke e power -ke t-e-ka t okay, so we have a 2 exponential term this is relating to elimination from the plasma, this is related to the absorption into the bloodstream. If you look at our old equation, if it is an IV bolus you are going to have only one equation like this, whereas if you are going to have oral dosage we are having these 2 terms.

So we have 2 ke and ka, ka is absorption rate constant, and ke is the elimination rate constant okay. So this is the equation we need to solve, so as a function of time concentration will increase because of k absorption, and then of course the elimination starts taking place so it will start going down like this okay, and of course at as the time increases okay there is no more absorption.

Now we can rearrange this t-max that is the time at which the maximum peak is observed by rearranging we can get logarithm of ka/ke*1/ka-ke okay. So of course as it sees ka has to be higher than ke that is very very important okay.

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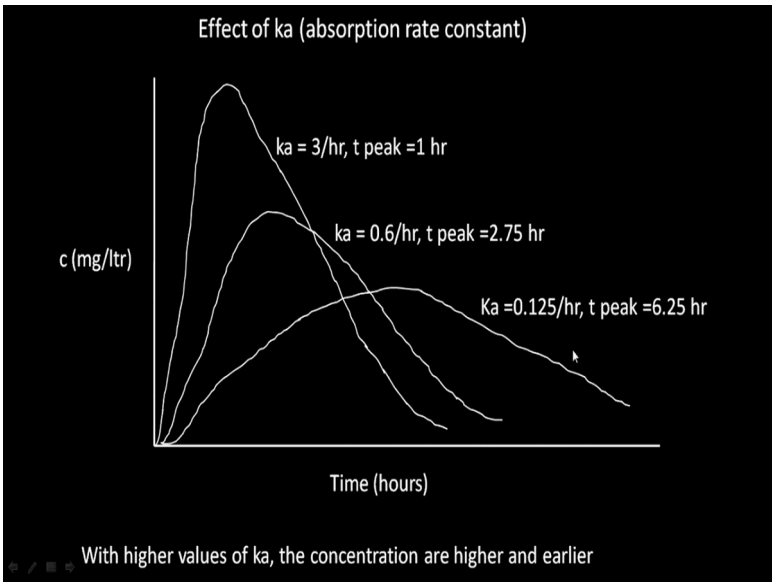

So how does they look if you have ka=3 hour - then the t peak appears first hour, if ka=0.6 that means absorption keeps going down okay it will start appearing much, much later. What it means is if the absorption of the drug in the GI is smaller, the absorption rate constant is smaller, the maximum concentration have starts happening much at a later time, later time, later time, and the maximum also is lesser and lesser and lesser, because elimination also starts kicking in okay.

So absorption has to be high to reach higher peak as well as at faster time, so with the higher values of ka the concentration are higher and earlier. So you need to understand, so if I want to have high peaks, and I want to have the peaks are appearing faster I need to have very high absorption rate constant okay.

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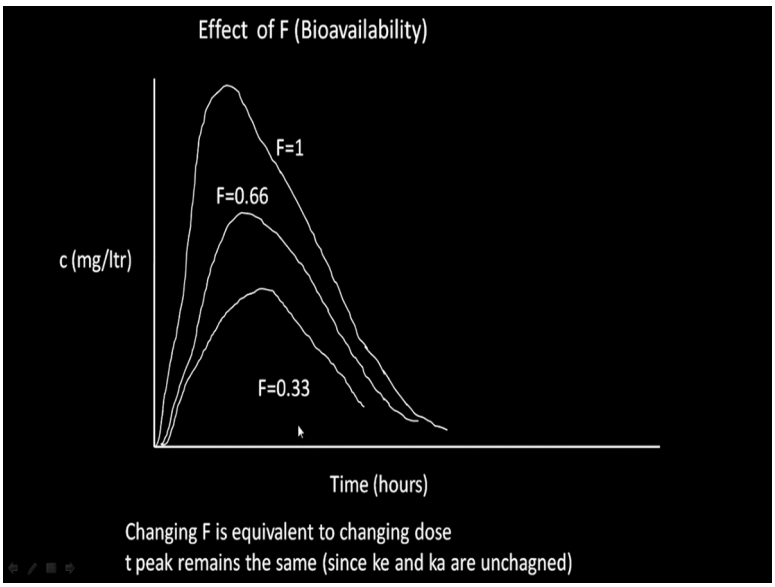

Now bioavailability, if the bioavailability is high that means maximum is 1, it happens like this the bioavailability is less, less, less, the maximum concentration keeps going down. So changing F is equivalent to changing dose, it keeps going down. The t peak that is a time at which the maximum happens is same, because we are not changing ke and ka but we are changing only F, so as the bioavailability decreases the maximum keeps going down.

But a time at which the maximum happens remains same okay, so this is a very, very important point to keep in mind, when you are designing drugs, pharmaceutics, dosing strategies all these can be looked at from these 2 simulation, these are simulations. By simulating this set of differential equation or simulating this equation for different values of these parameters okay.

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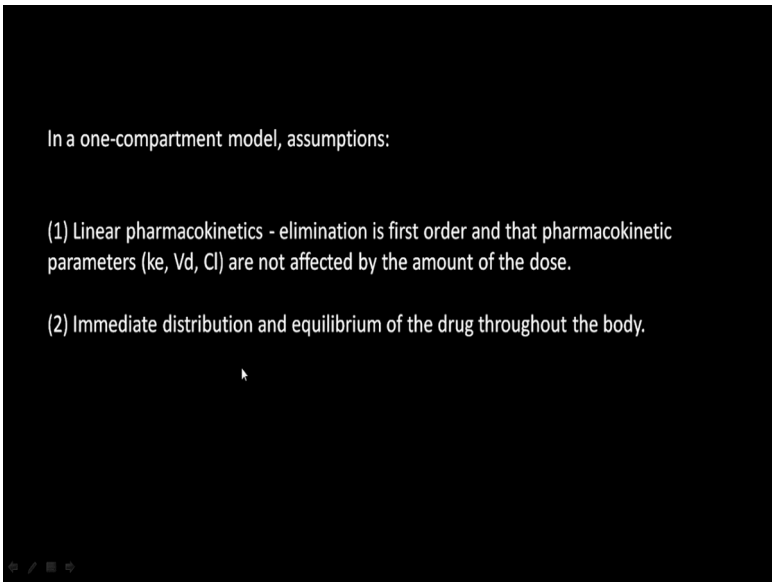

In one compartment model, we assume linear pharmacokinetics elimination is first order, and that pharmacokinetic parameters are not affected by the amount of dose okay. So we assume elimination is first order okay, and these numbers remains constant whatever be might dose concentration. Immediate distribution as soon as the drug is added immediately gets distributed and equilibrated throughout the body. So there is no time given for that to happen okay. These 2 are important assumptions in one compartment model.

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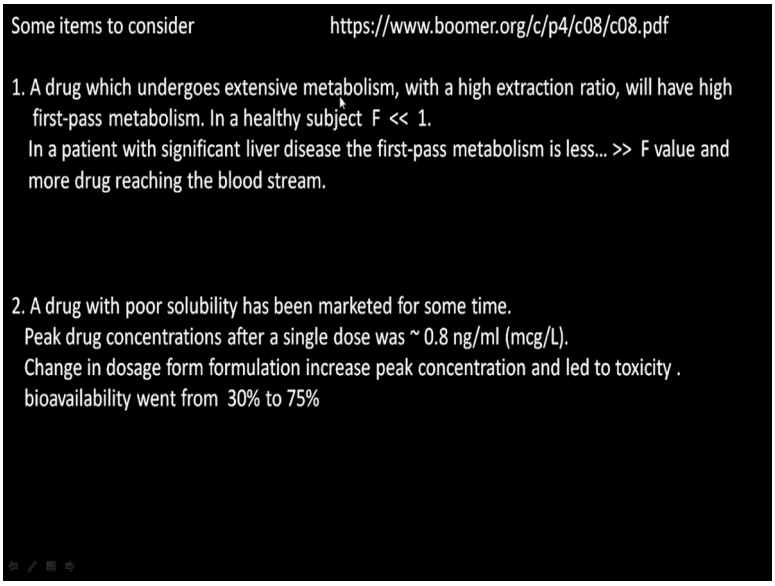

We need to consider some points this is a very interesting PDF have a look at it, from which I took out this information. A drug which undergoes extensive metabolism with high extraction ratio will have high first pass metabolism, so in a healthy your subject bioavailability will be

very, very low, because healthy subject extensive metabolism high extraction prayed okay, so F will be very, very less.

In a patient with significant liver disease the first pass metabolism is less, so F could be very high that means more drug will be there in the bloodstream. So the same drug on a healthy subject the bioavailability could be less, the same drug on a person who has some liver problem the F could be bioavailability could be high, so this is a very important point we need to keep in mind. The drug with poor solubility has been marketed for some time.

So the peak drug concentration after a single dose was 0.8 nanogram per ml that is the peak drug okay, that means like this you know peak drug concentration. But then they made a formation of this okay, so the peak drug concentration increased bioavailability went from 30 to 75 then it could become toxic, so nobody thought of that. So we may think that I will increase the bioavailability, I will increase the peak drug concentration, but it can also lead to toxicity, so you need to keep that in mind, this is a very important points okay.

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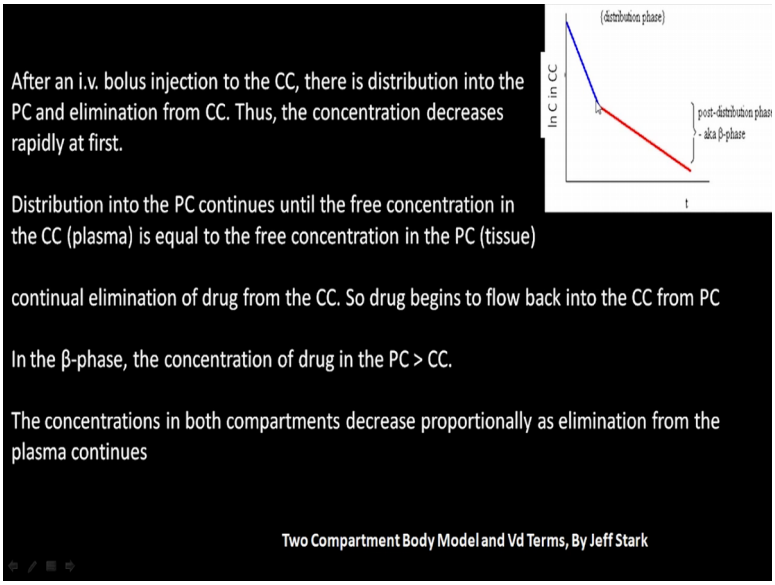

So go to 2 compartment model okay that means we assume tissues as another compartment your main plasma as one compartment okay, after an IV bolus injection there is a distribution to the tissue region, so that the drugs concentration decrease rapidly at first fast decrease, it is not the elimination but it goes and gets absorbed into the PC compartment that is the tissue compartment.

Distribution into the PC continues until the free concentration in the CC that is plasma is equal to the free concentration in the PC, once they get equilibrated flow of the drug into the PC happens, but once that equilibrates flow does not happen. Now the drug starts getting eliminated from the CC okay, so went through metabolism and all that, so as the drug constant gets eliminated concentration starts going down.

So whatever drug that is present in the PC will start flowing back into the CC okay, initially from CC it goes to PC and afterwards it goes from the PC to CC okay. So you will have this type of behavior, one fasts the sloping down another which is slow. So you will see 2 constants here rate constants here, so we call this the alpha phase, beta phase, concentration of the drug, and the PC will be very high than CC okay.

So then the concentration both the compartments decreases proportionately as elimination from the plasma continues. So you will see in the graph like this you know one fast drop and then slow drop, then you can be sure that there is 2 compartment system, so we need to consider a 2 compartment model okay.

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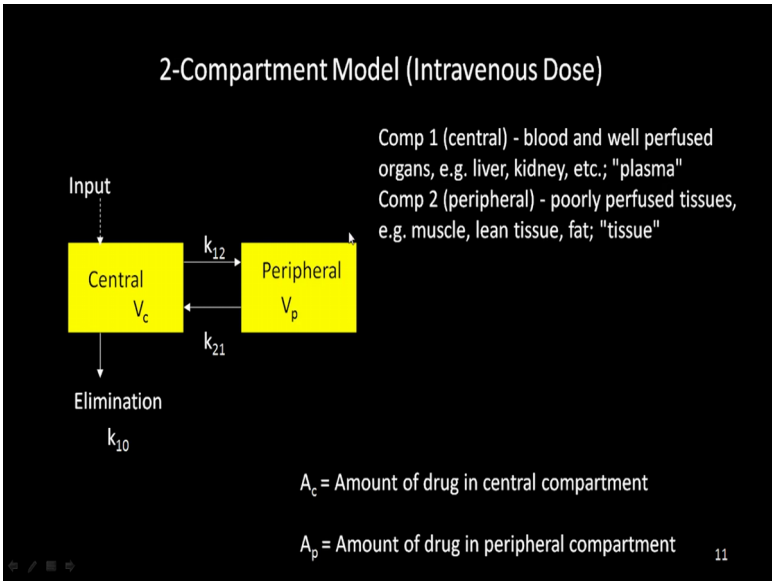

In 2 compartment model what do we have? You have a central compartment this could be your plasma, this could be your peripheral tissue and all other organs. So we can have an absorption here k12 and again coming back from the tissues k21 okay, elimination happens only here, elimination does not happen here only from the plasma that is the. So compartment one central could be blood and well perfused organs like liver kidney well perfused.

Whereas a poorly perfused muscle, tissue lean tissue, fat okay, so there is slow absorption, slow desorption. This could be the amount of drug in the central, this is the amount of drug in the peripheral region okay.

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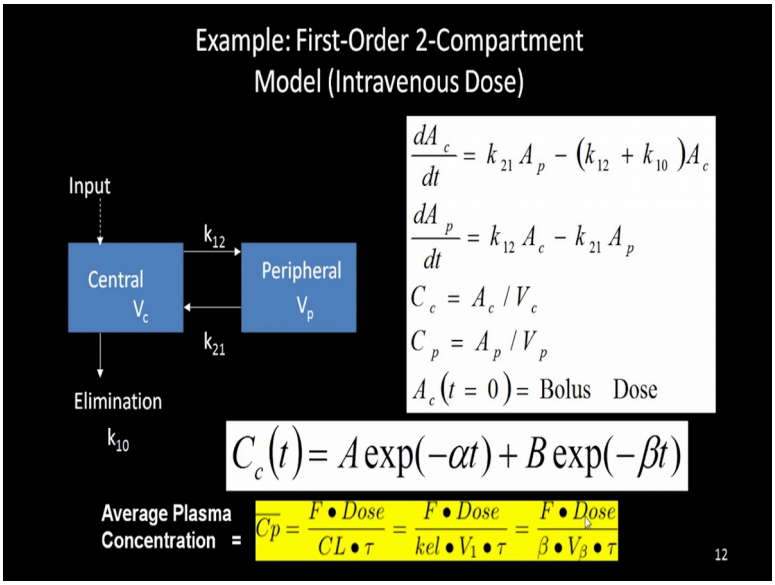

So when you do that we can have again write the mathematical model input elimination k12 going to peripheral k21, so drug in the Ac is coming okay from the peripheral region, drug gets eliminated from the k12 region, and then that drug gets eliminated because of thek10. Then Ap that is here, it comes in from the central to the diffusion, again it goes out through the diffusion okay. This is of course we are talking about the intravenous model.

So in one shot concentration is here, unlike the GI dose oral dose model we will look at that also. So intravenous model and it is a bolus okay, so this is very simple differential equations we can solve them no problem. So we get concentration A exponent-alpha t+B exponent -beta t, so alpha and beta can be calculated from this, and the average plasma concentration is given as F bioavailability dose okay, beta V beta tau and so on actually.

So this will have 2 exponent terms okay, because as I mentioned here so you have one here and one here, so for bolus so we will have these 2 terms okay, this is can be easily solved if you have some knowledge about calculus, I will not go into that okay.

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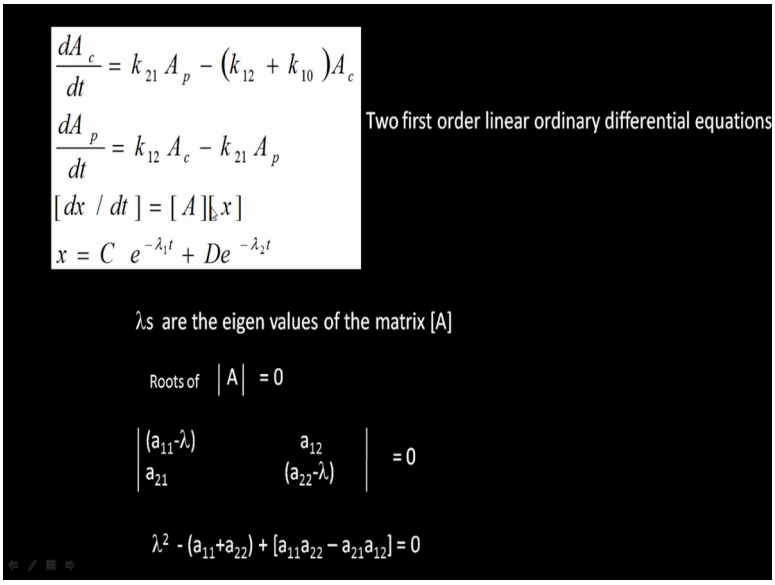

So if it is okay little bit of how to estimate this, this can be written as dx/dt=A x, and the solution for this type of linear first order differential equation is given like this, e power-lambda 1, e power-lambda 2, lambdas are called the eigenvalues of the matrix A, how do you get it? Roots of the determinant A=0, A is a is given by a11 that is the term first term in the matrix, this is a second term, this is the third term, this is the 4th term.

So you write this eigenvalue equation you get lambda square and so on okay, sorry there is a lambda here as well okay, there is a lambda here as well so let us put that into equation okay. So we can solve this equation, this is a second order quadratic equation, so this will have 2 lambdas, lambda 1 and lambda 2, so x is given by like this equation C and D depends upon the initial value. So this is a little bit of background of how or why you get this type of relationship okay.

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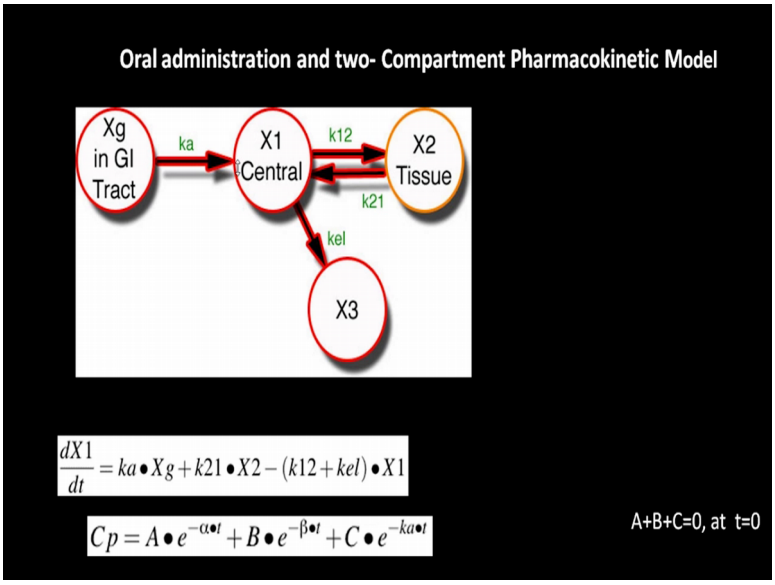

So if it is an oral dose of course we need to again consider ka absorption, again we have a central compartment, this is the elimination part of it, so we get an extra term here okay, remaining portions remain the same. But we get an extra term with A coming into the picture okay for the central, whereas for the tissue it does not change. So we will have a concentration in the plasma we will have 3 terms, so one term corresponds to the ka that is the absorption part.

And these 2 terms as I mentioned here okay, these 2 terms here okay. So for a 2 compartment model we will have 3 exponential things coming in, these 2 correspond to the elimination, one fast elimination and other slow elimination, this relates to absorption okay that is how the model look at okay.

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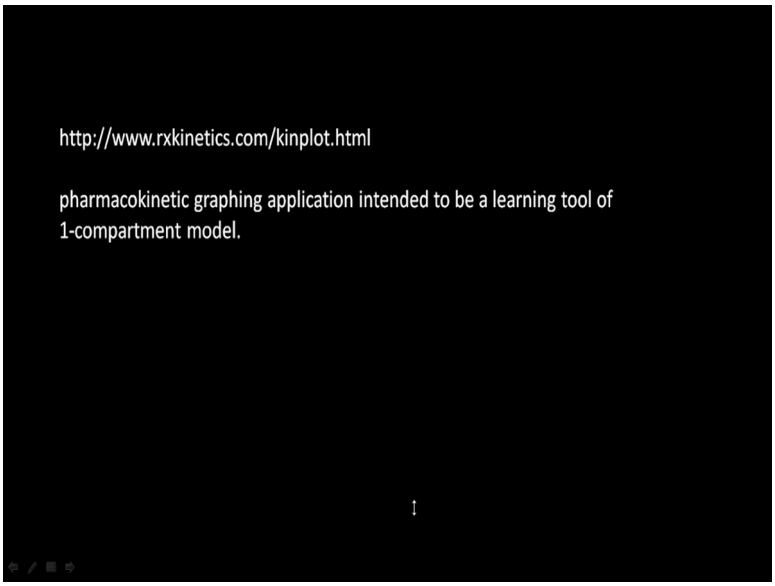

So in fact we can it is a very good learning tool for one compartment model okay.

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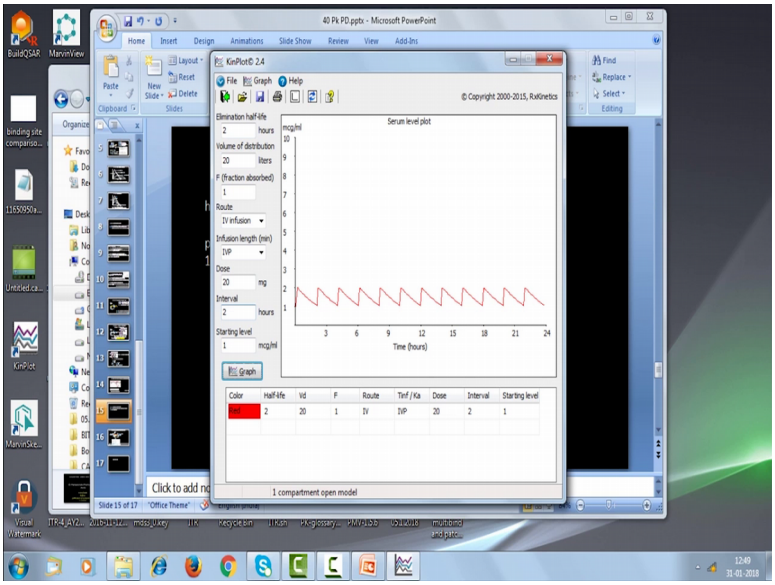

So we can get different values here, it gives you the interval 0, half-life is missing and half-life is towards volume of distribution is 20 litres okay. So concentration of the drug goes up down, up down like that because we have decided that it will be like a every 2 hours dosage is given actually. So I am if the fraction goes down we can model that also okay you can see that, and because your bioavailability.

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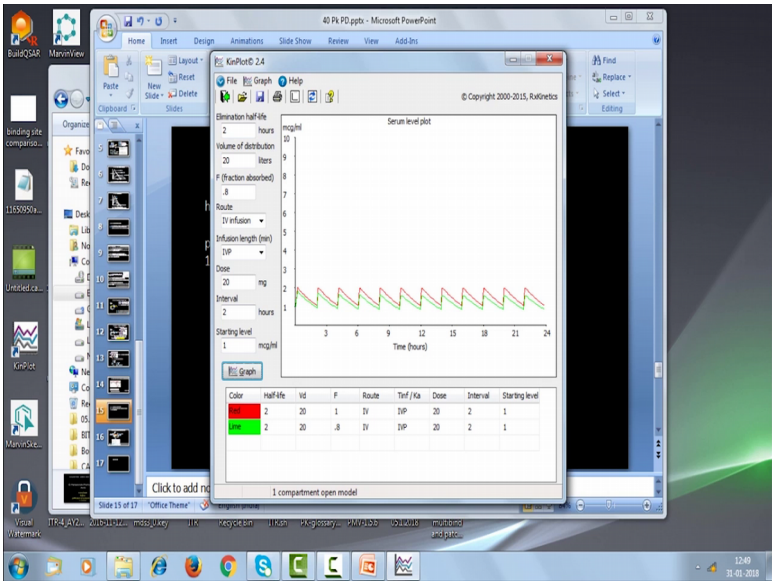

This is a nice simulation graph which we can have a look at this is based on a one compartment model okay, it is called KinPlot okay so I am not going to that okay.

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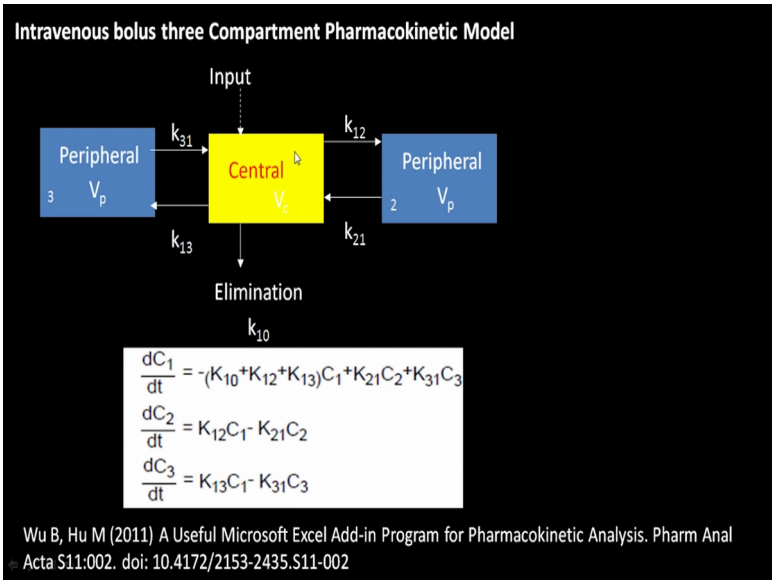

So we can again have 3 compartment model of course, so we can have 2 peripheral regions okay, this could be your central plasma. And then you could have region 2 peripheral region, region 3, so we can have k12, k21, k31, k13, and then elimination of course happens only in the central compartment. So we have concentrations of the drug C1, C2, C3, so we have 3 differential equation, this is a IV bolus, so we do not have the absorption here okay.

Like that if you want to include the oral, then we can have the ka term also coming into this, and then we can solve these differential equations very simply okay. There is a very useful Microsoft Excel add-in program for pharmacokinetics analysis okay, you can have a look at this software, this software can calculate many 1 compartment, 2 compartment models for different values of your rate constants okay.

And we can do this even in Excel, because we know that for a one compartment model we have for oral dose this is the equation we need to solve so we can use Excel. For a 2 compartment model sorry, for a 2 compartment model intravenous okay, this is the model for 2 compartment model for IV sorry for oral dose, this is the model. So for different values alpha, beta we can simulate what to be the concentration in the central compartment.

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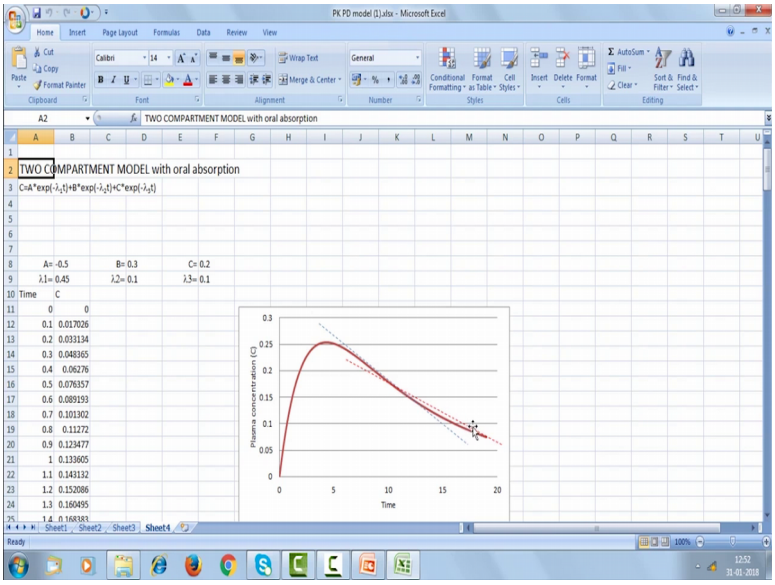

And I have tried to do it in excel as well, I would like you to I will show you that okay, so this is the 2 compartment model okay with the oral dose. So we will have one relating to your absorption, and the other 2 will be related to faster elimination, slow elimination. So as you can see here plasma concentration how it goes up, so initially you have a very fast drop okay you can see here fast drop, and then you have a slow drop okay fast drop here and then slow drop here.

So fast elimination, slow elimination because of that peripheral. So we can play with the different values of A, B, C and then we can change this lambda, so we give the equation here okay, we can simulate it so it is very. So this is the 2 compartment model with the oral absorption okay.

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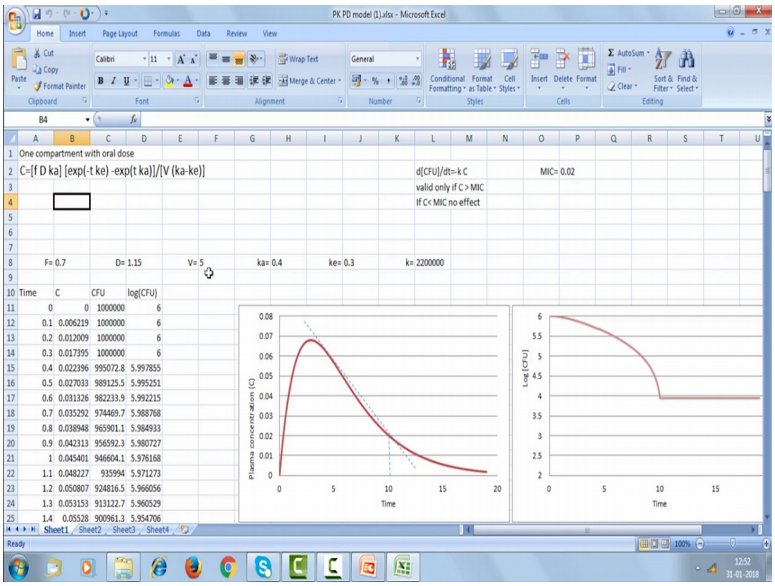

So this is one compartment model with the oral absorption, so this is the equation if you remember one compartment model ka is the absorption term sorry, ka is the absorption term and then ke is elimination term okay. So we can look at F, F D is the dosage, V is the volume of distribution, ka, ke, so this is one compartment model you can see this okay, this is one compartment model. And this is the 2 compartment model oral absorption.

So we have 3 lambdas in a one compartment model, we have k absorption and only one exponent term come here okay.

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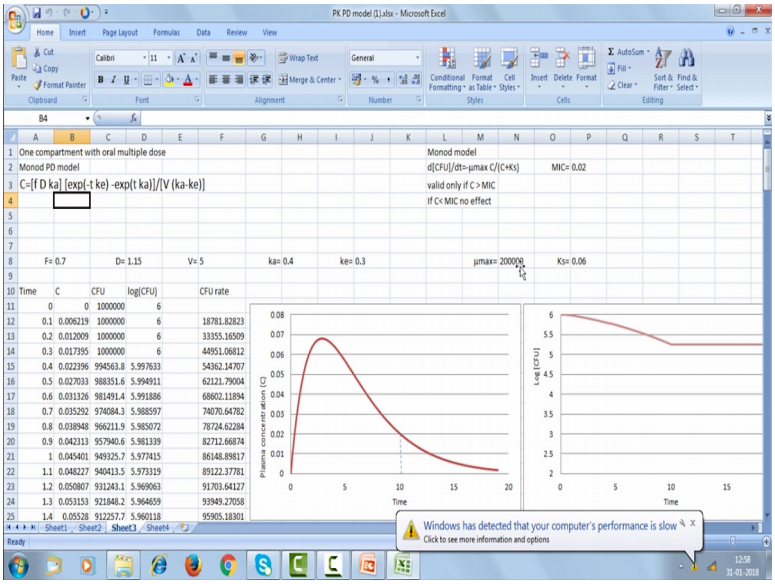

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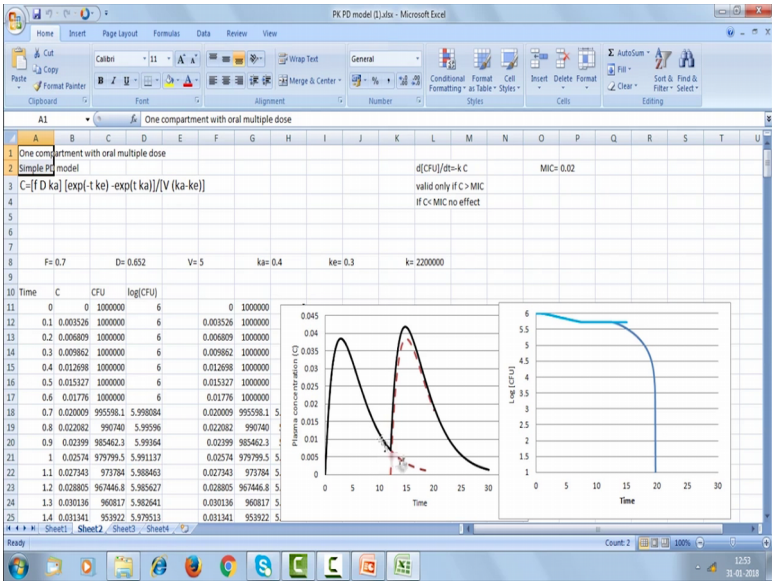

Then we want to suppose we have multiple doses okay, I am giving doses after every say 12 hours, so concentration goes up and then it starts getting eliminated, again I give these are

oral multiple dose, again the concentration goes up okay as you can see here. And the advantage of given multiple dose is seen as you can look at the black colour, it is slightly higher than giving single dose.

Because you already have some drug little bit left, and when you are adding one more dose concentration, that is why sometimes if you keep giving more doses continuously there is slight build up okay, accumulation and you will see better response, because of that accumulation. So the first dose max is here, if you do not consider this build up, you will always get the same maximum concentration C-max.

But because some drug is still present when you give another dose it becomes higher. So when you give another 3rd dose you may get much higher, so you continuously you will keep getting higher and higher as we keep giving doses. So you can simulate the one compartment model with oral multiple dose also as seen here okay. Now we can also involve PD that is pharmacodynamics, so we know the concentration.

So imagine we are giving an antibacterial drug, and if the d CFU/dt=-k C that is CFU that is the bacterial load that is colonies these depends upon the concentration okay, colony keeps going down depends upon the concentration of the drug that is present in the body. And it is valid only when the concentration is >MIC, MIC is minimum inhibitory concentration, if the concentration is very low, suppose we assume MIC=0.02 you can see here.

So at these concentrations the drug will not be able to kill the bacteria, because as you know as per definition only if the concentration is above MIC it will kill the bacteria, so if it is here in this region it will kill the bacteria otherwise it will not kill the bacteria. So simple model I have taken, the killing is proportional to the concentration of the drug, but it is valid only if it is above MIC. So when we do that and then when we do the look at the CFU, imagine initially you have logarithm CFU as 6 that means 10 power 6 colonies.

So in this region bacteria is getting killed in this equation, so the bacterial colonies keep going down, but then after that the drug does not act so the bacterial colony remains at 4 only, that means log CFU=4 that is 10 power 4. So by one single dose you are able to reduce from 10 power 6 to 10 power 4 okay. When you do multiple doses like this, so you give 10 power

6, power 4, but imagine you are giving the second dose quickly it comes in so again it starts acting.

So it is act from here, the drug acts, acts, acts, and then only for a short region it does not act, but again it starts acting as you can see here. So the colonies as soon as you give the second dose, the colony is become very, very low actually as you can see here. Because a drug concentration inside the body remains at above MIC for a very, very long time as against here, because after this drug concentration has come down, so there is a reaction assuming a simple model like this.

We can make Monod type of model also okay, CFU/dt=-mu max, as you know Monod equation mu max C/C+Ks, C is the concentration of the drug, again it is valid only when C>MIC, like that you know so you get that different type of graph as against this type of graph okay, when use assume a Monod equation. So we can for a PD we can think of different types of model of drug action on the cells or bacteria or whatever it is okay.

So what based on the concentration of the drug in the plasma we can incorporate the PD model. So this is the PK model, this is the PD model. So in the PD model we can make it as a very simple model first order killing model or we can incorporate Monod type of equation also okay. So these PK PD equation can be easily modeled using Excel, so you do not need a great software for this.

And all you need to consider as you know I mentioned for a one compartment oral we have this equation, where a single oral does we have this equation, so it is very simple to model in Excel. And for a 2 compartment oral, this is intravenous dose, you have this equation, so it is very simple to model both the situation as I have shown you, this is the 2 compartment model here, and this is the one compartment model here as you can see here.

So PK PD can be easily modeled as I have shown here okay. So we have looked at lot of things in the past 40 lectures okay. We have talked about how do you make use of computation tools for drug design, we looked at huge number of databases, we looked at structure drawing softwares. We looked at how to determine or calculate various descriptors, these descriptors are very useful, because when we try to develop the quantitative structure activity relationship we need these descriptors.

We looked at how to do regression, relationships, connecting descriptor or structural features with activity, we called it a QSAR. Then we looked at 3 dimensional QSAR, where we bring in the conformation part of the system. Then we looked at pharmacophore modeling, pharmacophore are special features which is molecular structure has like hydrogen bond donors, acceptors, hydrophobic and so on.

So we have few structures we know how to calculate or how to determine the pharmacophore features, we can screen databases to see whether such other molecules have this type of pharmacophore features. We also looked at how to calculate the structural descriptors using semi empirical quantum mechanics like electronic fat, electronic energies, like highest occupied molecular orbital energy, lowest unoccupied molecular orbital energy and so on.

Then we looked at target based drug design, where we have the target protein, 3D structure is known, so we can dock the ligand to the target, and see how they bind. So we looked at different softwares for target based drug design. And we also looked at how to look at common features of various proteins, in case you want to understand if there is going to be a cross binding of a ligand into various proteins.

And then finally we looked at the pharmacokinetics that means what the body does to the drug one compartment model and 2 compartment model with oral dosage. Then pharmacodynamics where the drug does to the body, that means cells or tumor or bacteria, fungal okay. So you look at the large number of software which are freely available, downloadable softwares or through web servers, you do not need any commercial software to learn this particular course.

Please remember that we looked at a huge number of softwares and all of them are free for academic, all of them many of them are downloadable, many of them could be run through server you get the results into your email and so on. And then all these softwares are extremely good we can use it for our research purposes, we can use it for our academic purposes also, so we do not need any commercial software.

And all these softwares are developed by professors from various universities, so they have a high level of standing okay. I hope you enjoyed this course I hope you have benefited and

you can make use of all these databases and software's for furthering your research or furthering your knowledge. I am sure there are many more software's available apart from what I have showed you okay.

So I hope you have a good time, I also hope you had a good time solving all these assignment problems okay, good luck to you, and all the best. And thank you for going through all these lectures and videos okay, thank you very much.