Drug Delivery Principles and Engineering

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Lecture – 01
Drug Delivery Introduction and Pharmacokinetics

Hello everyone, this is the new course called Drug Delivery Principles in Engineering. I am Rachit Agarwal, I am an Assistant Professor at Indian Institute of Science in the department of Biosystem Science and Engineering. And will be offering this course, which will essentially go over some from the principles of drug delivery, why is the drug delivery required? Why are we making this as a different format of a course and what are the different engineering aspects we can add to it so as to get more efficient delivery?

Ultimately the major purpose is to improve the life of the patients. Let us say, if a patient is coming with the disease, we want the patient to get cured as quickly as possible, without having any major side effects. So, the current drug delivery is great. We have helped lots of patient with the current drug delivery, but then what also happens is in a lot of cases; you see lot of side effects being present; such as, in chemotherapy you see patients are suffering, they are losing their hair, their immune system is weak, their quality of life is going down.

So, what are the different things? Engineering aspects we can bring to it. So that, these things the side effects are lower as well as the efficacy is higher.

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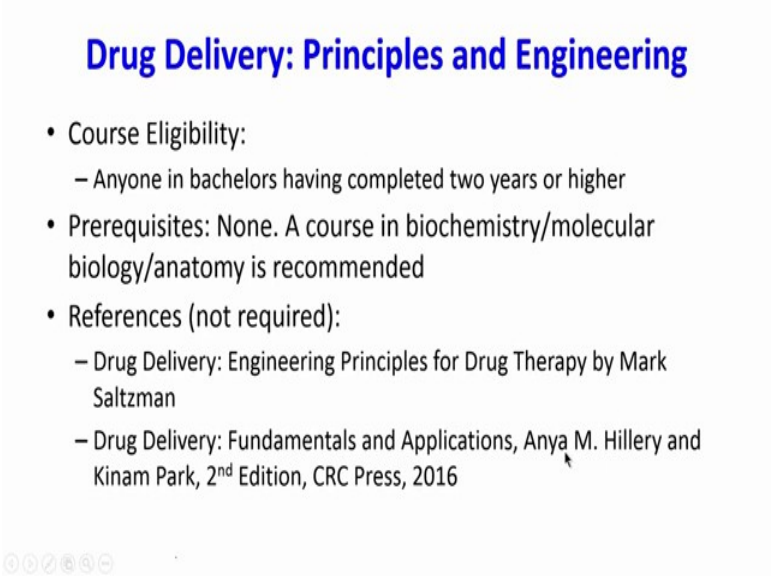

So, some of the quick things about the course itself. So, the course eligibility this is open to anyone in bachelors, who has completed his two years or higher or this is also open to anybody, who is in pg or in some other form of postgraduation. There are really no prerequisites to this; it will be; it will be good if you have some basic background of biology.

So, any course in biochemistry, molecular biology, anatomy is recommended, but again its not required. Well, as we go through the course, we will give most of the information that is required for whatever we are teaching here. References again these are also not required these slides well contained most of the material, that you will need to understand this course, but and there are a couple of good references that you can refer to if you want to gain some extra knowledge on this.

One is a book by Mark Saltzman this is Drug Delivery Engineering Principles for drug therapy, its a very good book and then, another is the Drug Delivery Fundamentals and Applications by Anya Hillery and Kinam Park. So, these are the two books that are recommended, but again are not required for this course.

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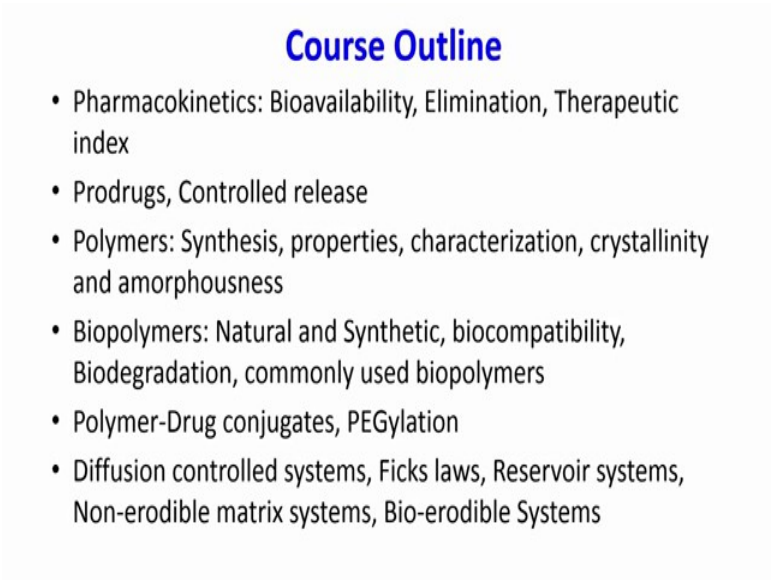

So, I will just go briefly over the course outline and how this course is going to go over the next few weeks. So, during the start of this course, we will talk about pharmacokinetics and that, typically involves the bioavailability of the drug, the elimination of the drug and how therapeutic the drug is and will go over these terms in due time in the course.

Then will talk about pro drugs and controlled release of these drug molecules some more engineering aspects will start coming in at this point of time. We will talk about various polymers and we can use, how they are synthesized? What are the properties of these polymers? How do we characterize these polymers once you have synthesized them? The crystallinity and amorphousness of these polymers will also be discussed. Then we' ll go into biopolymers. T hese will be polymers, that we can use for bio applications, these can be both natural or synthetic.

We will talk about their biocompatibility, when to use what? As well as, their bio degradation and some of the very commonly used biopolymers in the field. As we move forward we will talk about polymer drug conjugates, another engineering strategy to enhance the drug efficacy; some of the major examples there include pegylation. And then, we will talk about diffusion control systems. This will include some basic knowledge of Fick's law; reservoir type systems, non erodible type systems; again these

are some of the engineering systems that we will use to enhance our drug delivery and we will describe them as we go along.

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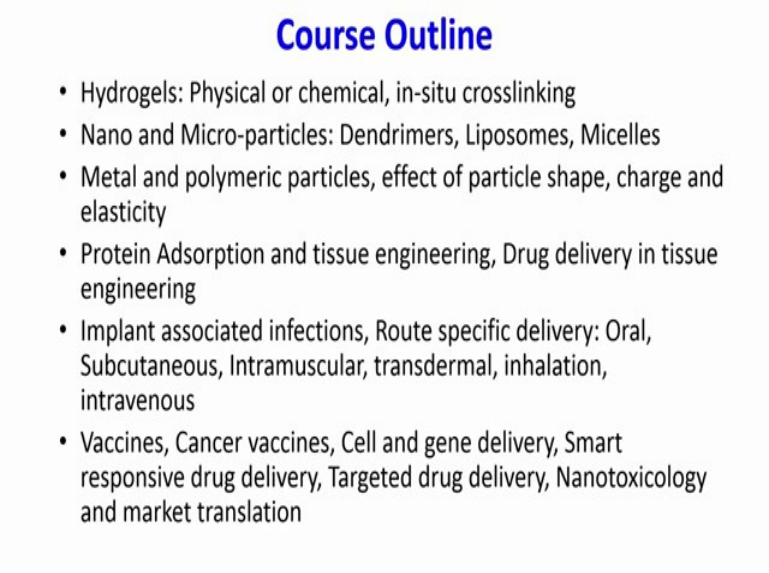

And in the second half of the course, we will talk about hydrogels, again another format of delivery. So, hydrogels can be both physical or chemical getting in situ cross linking, so, the delivery in hospitals may be improved. We will talk about nano and micro particles some of the big hot words these days; some of the major ones including dendrimers, liposomes, micelles along with the polymeric particles. Will also talk about metal in polymeric particles, what is the effect of shape of the particle? What is the effect of charge of the particle and elasticity of the particle? When this particle is traversing through the body? Will talk about, protein adsorption and tissue engineering. This is very important, because all tissue engineering application is required some or other delivery to improve the tissue properties.

So, this could include cells, this could include drugs, this can include some other proteins. So, we will talk about that. Then we will talk about, implant associated infections; if you put anything in the body, that is susceptible to getting infections. So, how do we prevent that? How do we proactively ensure that these implants do not get infected? Will talk about route specific delivery. So, these could be oral route subcutaneous several of them.

So, we will talk about, when to use which route? Which will be needed for different applications? And then, towards the end of the course, we will talk about vaccine delivery again one of the major success of the current drug delivery; cancer vaccines, cell and gene delivery. So, if you are only looking to deliver cells or certainly not. So, genes, how do you deliver them? What are the challenges associated with that? We will talk about smart responsive delivery? How do we make them smart?

So, maybe you want it to only come out at a certain time or maybe you want it to only come out when we give them certain triggers. So, we can kind of engineer those drug delivery systems as well. And towards the end of the course, we will talk a little bit about, nano toxicology and how you can lead to market translation of whatever these research products that you are developing through this course..

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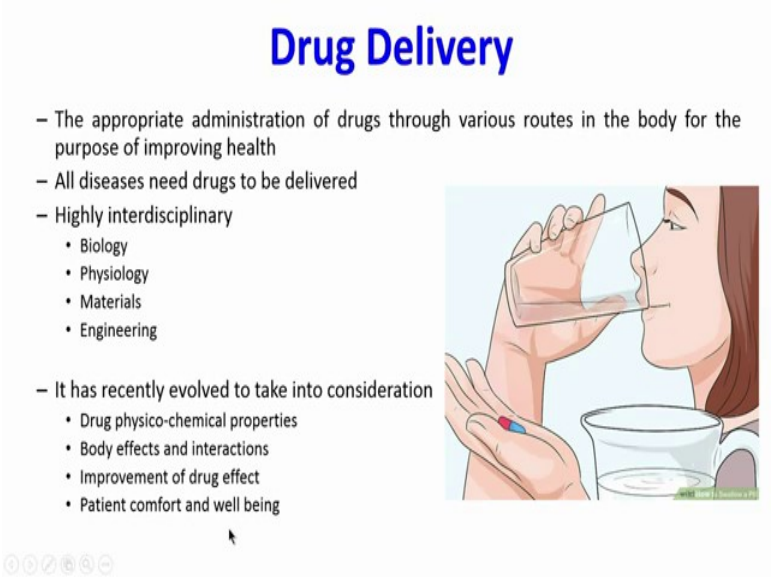

So, let us start into the course. So, what is drug delivery? As you can see from this picture is essentially nothing, but administration of the drug; of course, in this particular picture it is been shown that, this is being administered through an oral route; however, the route can be chosen depending on the application. And nearly, I mean, almost all diseases need some kind of drugs to be delivered; these could be painkillers, these could be chemotherapeutics, these could be some other form of the drug, but nearly all applications of drug delivery is directly ready to treatment of a disease.

The field is extremely interdisciplinary this involves several different kinds of subjects, that may include biology, physiology of the body, the materials, that will talk about extensively through this course and then of course, engineering them, so that, they can be more efficiently delivered in the body. And then it is also recently evolved to take into consideration several factors, which is drug physico chemical properties.

So, how is the drug going to interact with the body? What are the chemical properties? The body effects and interactions. So, how does the body respond to a certain drug? How can we improve these drug effects? And then ultimately the major goal the milestone, we are looking for is to ensure patient comfort and well being and making sure that, patients are not suffering from side effects and getting cured as quickly as possible.

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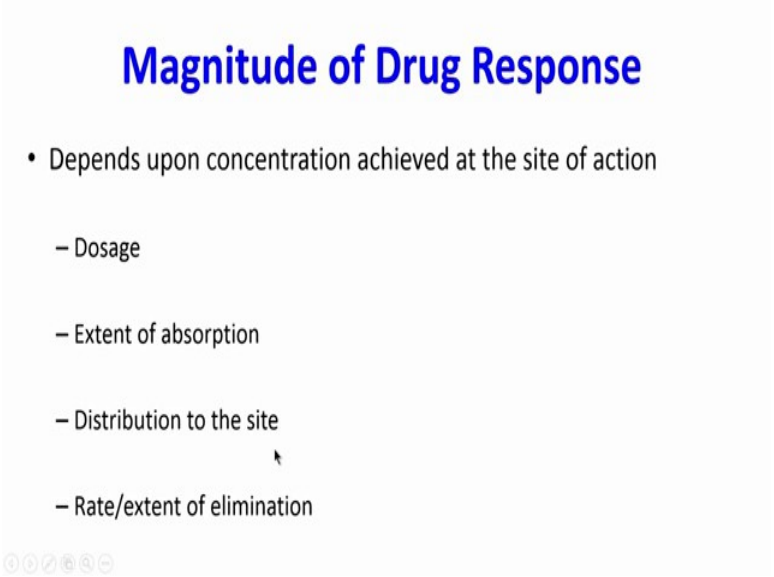

So, the magnitude of drug response again depends on, how much you can achieve concentration at the side of action? So, let us say, this is a wound which is on a skin, maybe we got into an accident and we have a small cut on the skin, at that point there is really no need to deliver the drug throughout the body; all you want to do is just local application. So, it is very important to achieve high concentration of the drug in the site of action, that may be required to treat that particular illness or particular disease and then, not give it everywhere, where made it may cause some harmful effects some side effects.

So, again all of this will depend on dosage; as I just mention how much you can deliver and how much is required? What is the extent of absorption? So, how much the drug can get absorbed in that site? So, unless the drug is absorbed and becomes bio available; essentially meaning that, it is in the system for it to act, the drug will not be useful. How it distributes to the site?

Again related to absorption, once it gets absorbed; let us say, if it is in the whole lever then, the drug has to diffuse and distribute throughout the whole lever and then ultimately, you do not want the drug to be there all the time; once you are cured, you want the drug to also get eliminated. So, what is the rate and extent of this elimination of the drug?

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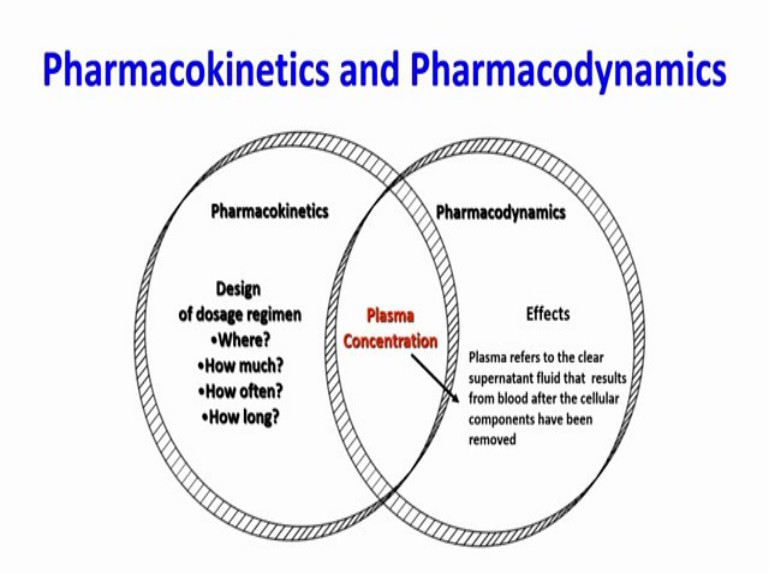

So essentially, there are two major components of any drug delivery. These are pharmacokinetics and pharmacodynamics. So, as the name suggests, pharmacokinetics is essentially the design of the dosage regimen. So, where do you want to give it? How much do you want to give it? How often do you want to give it? And how long do you want to give it? It may include several other things, but these are the major criteria that, before you even go into the body you want to ensure that you know the answers of these things for a certain application.

So that, you can decide what are the different characteristics of a drug that you are looking for? All of this is going to lead to a certain plasma concentration; if it is needs to

distribute throughout or even if it is given locally, these drugs will diffuse into the plasma. And once it goes into the plasma or the site of action, then the pharmacodynamics comes in, where the next questions we are asking is what are the effects of these drug once it reaches the plasma? So, how it interacts with a certain receptor that the drug may be binding to? How the body is interacting with these molecules? How it is being degraded? So, all of these are essentially pharmacodynamics.

So, for the purpose of this course will essentially focus on pharmacokinetics and then try to improve the pharmacokinetics of the drug; the pharmacodynamics is a separate field that, we are not going to talk about in this course, but you will see me talk about a little bit throughout the course, but the major focus will be on the pharmacokinetics.

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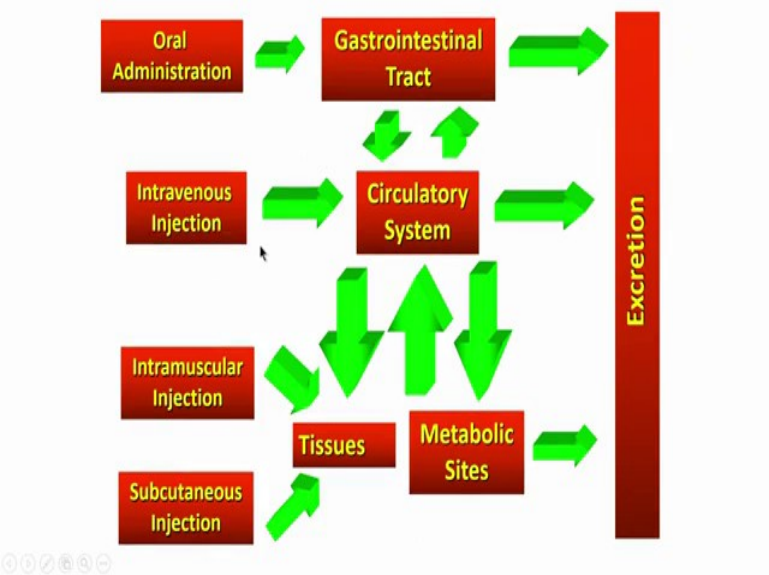

So, this is again a complex graph, but essentially depicting what was depicted in the last figure? So, you can treat the drug through several routes and again, these are not the only routes that, we are limited to there are several others, but these are some of the major ones. So, you can either take the drug orally; once you take it orally, it is going to go into the gastrointestinal tract; basically, your stomach an intestine and from there it can either get excreted or it can get absorbed and go into the circulatory system, which is basically blood.

The other way is, you can either give an intravenous injection, which will directly lead the drug into the blood and from there, it can again either get excreted or from the blood,

which goes everywhere in the body; it can go into the gastrointestinal tract as well as other tissues in metabolic sites. The same type of pharmacokinetics is seen with intramuscular injection you give it intramuscularly, typically at a certain region it may be on your thighs, it may be on your biceps. So, the drug is going to go directly into those tissues and from there the drug can then diffuse out into the circulatory system; can get excreted; can be metabolized and then, get excreted and the same thing applies to the subcutaneous system.

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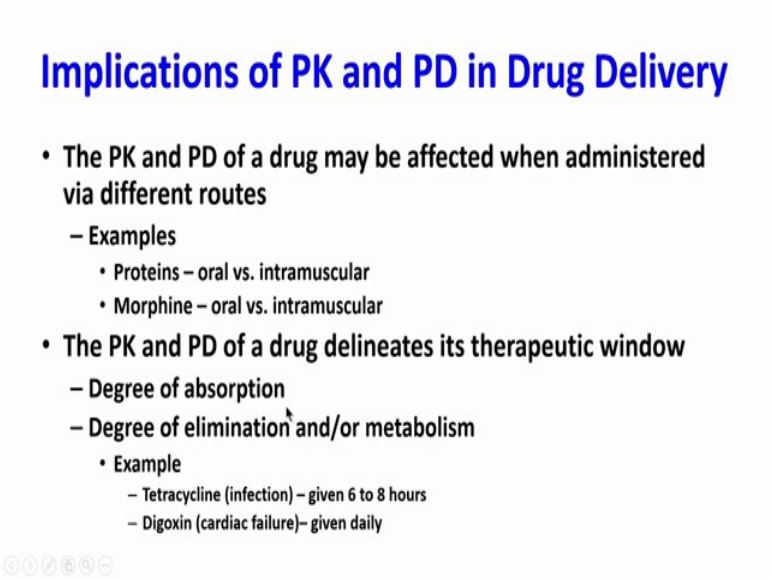

So, then what are the implications of this pharmacokinetics and pharmacodynamics in drug delivery? So, first thing is the drug may be affected depending on what route it is administered in? So, again if you give something; let us say, if you are trying to deliver proteins; if you give it orally versus intramuscularly they may have different activity once they reach the blood because these proteins are fragile molecules if you give them orally and they have to go through the gastrointestinal tract your stomach, which is a very low pH that, would lead to denaturation of these proteins and maybe the drug may not be active versus if you give it directly intramuscularly for let us say some muscle pain then, these protein may be much more active as well as much more available at the site. So, these are some of the examples here. Another example is morphine the same considerations here, where exactly you want to give it and then, essentially the PK PD of a drug delineates the therapeutic window, that it is going to work in.

It is going to give you an idea of how much of the drug is going to absorb? So, let us say, if I say that, if I give a drug x, 100 milligram of it, only 10 milligram of it gets absorbed, then that helps me then, define as to how much drug should I give? Because if I want finally, in my blood the concentration of total of 10 milligram then, 100 milligram is ok, but if I give less than that, then I would not be able to get to that therapeutic levels it may be required. And then of course, it also tells you at what rate its eliminated or metabolized?

So, let us say, if a drug is getting metabolized very quickly then, you will have to take it again and again in short periods of time. For example, in infections, tetracycline is given every 6 to 8 hours whereas, another in another example a cardiac failure drug digoxin is given daily. So, this is on the basis of how much of the concentrations you want in the plasma and how fast it is getting cleared away from the plasma?

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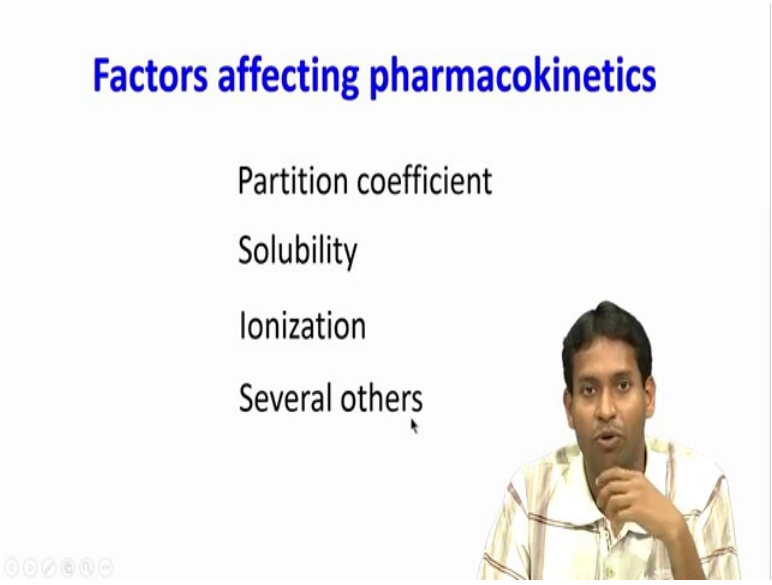

So, again there are several factors that, affect pharmacokinetics. I have only listed three here, but there are several of them and we will discuss these major ones in a little more detail in upcoming slides. So, these are partition coefficient, solubility, ionization and again several others. So, let us talk about each of them one at a time.

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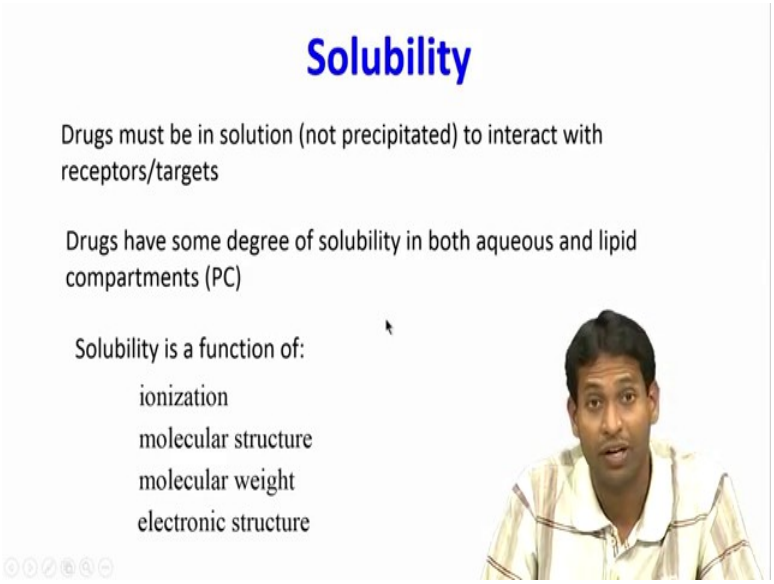

So, starting with solubility; so, drugs must be in solution right; I mean if the drugs are not in solution, they are in precipitated form, they cannot get solubilized in the bio fluids and flow around, then they will not be able to interact with the receptors and targets. So, the solubility of the drug is must; if it has to act and then, again drugs may have some degree of solubility in both aqueous as well as organic solvents.

So, in this case lipid compartments and the ratio of this is called the PC, the partition coefficient and we will talk about that, again in upcoming slides. So, solubility is a function of lot of things; typically, the things that are charged have much higher solubility in water; the molecular structure, how hydrophobic and hydrophilic it is? How big is it? So, to lead to the molecular weight and of course, the electronic structure also tells us, how soluble it could be in the water?

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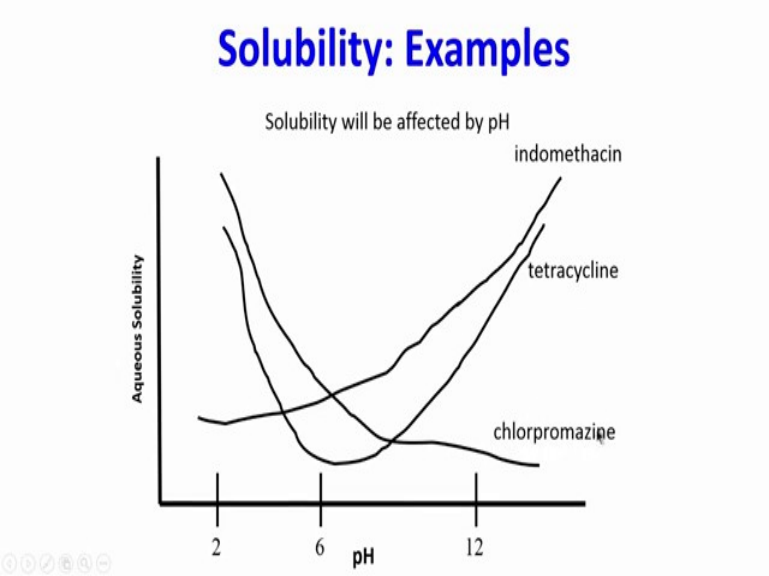

So, here is an example, here are three drugs; you have indomethacin, tetracycline and chlorpromazine and here is the aqueous solubility with respect to the pH. So, you can clearly see that, the pH affects the solubility as well as even at a single pH. Let us say, the pH of 6; you have drugs which have different solubility. So, again this helps you then, these parameters are required for you to know, that how should you administer each of these drugs. So, let us say, if I want to put something directly into the blood, which has a pH of 7.2 to 7.4 I and I want a high concentration of this particular drug, I cannot do that, just because this drug has very low solubility at a pH of 7 and if I inject it in the blood it is going to precipitate out, which is not good because, that may cause blockage in the arteries and veins leading to strokes and other problems.

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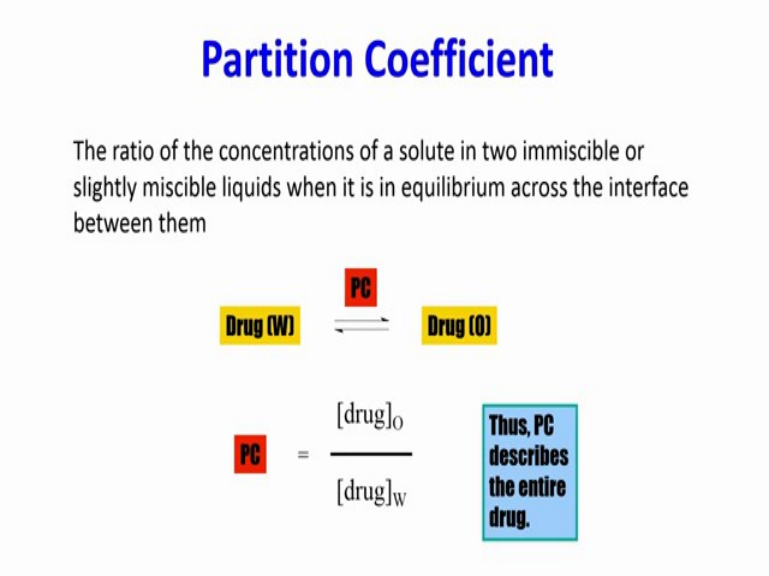

Partition coefficient another major parameter, that is required for you to know before you, even attempt to use the drug and this is really nothing, but its the ratio of the concentrations of that particular drug in two immiscible liquids.

So, this essentially defines what is equilibrium of the drug between the interface of these two liquids? So, if I express it mathematically; we are essentially saying that if I have two immiscible liquids the drug may have a certain concentration in water and a certain concentration in oil and this is essentially in equilibrium with each other.

$$PC = \frac{[drug]_O}{[drug]_W}$$

So, PC is property of a drug; it is not going to change with the amount of the drug; it for a molecule x the PC will remain constant regardless of what is the amount and things like that.

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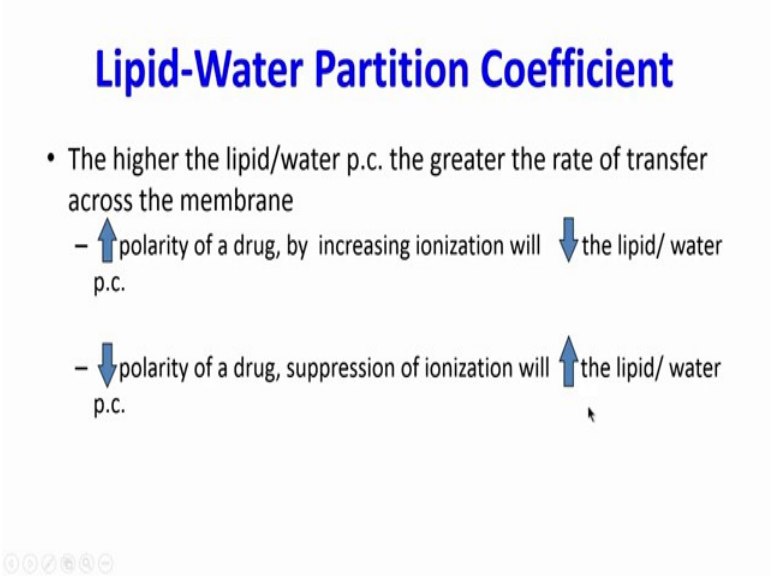

So, essentially what we are saying is that the higher this lipid to water the ratio the greater is the transfer across a membrane. So, membranes are lipids. So, if you want the drug to diffuse in through the lipid membrane then they need to have higher lipid to water ratio. So, essentially higher partition coefficient.

So, in this case, we are saying that, if the polarity of the drug goes up, which means that it is increasing the ionization which will essentially mean what? That the solubility in the water is also going up. So, if the solubility in the water is going up then, this partition coefficient will go down and that essentially means that, is diffusion across a lipid membrane will be lower although it will be highly soluble in water. Similarly, if the polarity of a drug is going down, which means that, it has lower ionization, then it solubility in the water will also decrease increasing the partition coefficient, which essentially would mean that these drugs will be fairly well soluble in lipid components and will be able to diffuse through the cell membrane.

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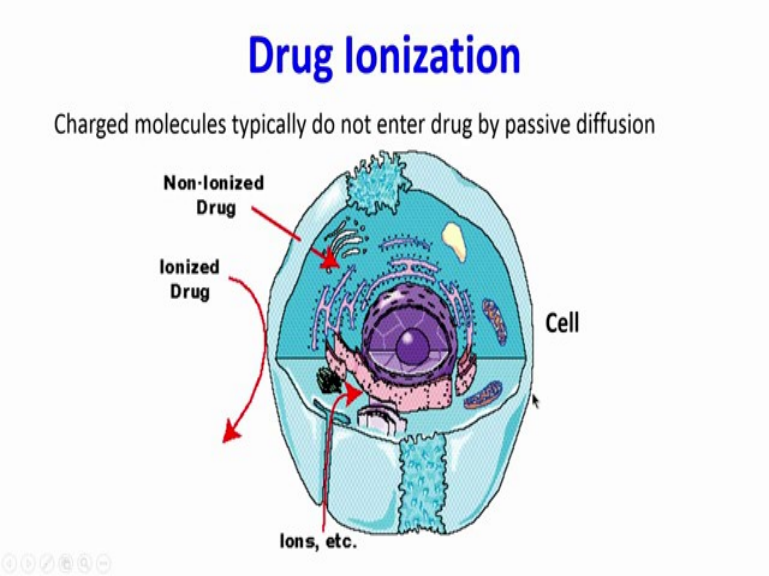

So, this is represented here through picture. So, you have charged molecules and typically, these lipid membranes are very good at repelling the charged molecules. If you have an ionized drug coming in; those drugs will not be able to go into the cell membrane. However, if you have non ionized drug and it is fairly hydrophobic with the high partition coefficient, then it will be able to diffuse through the cell membranes.

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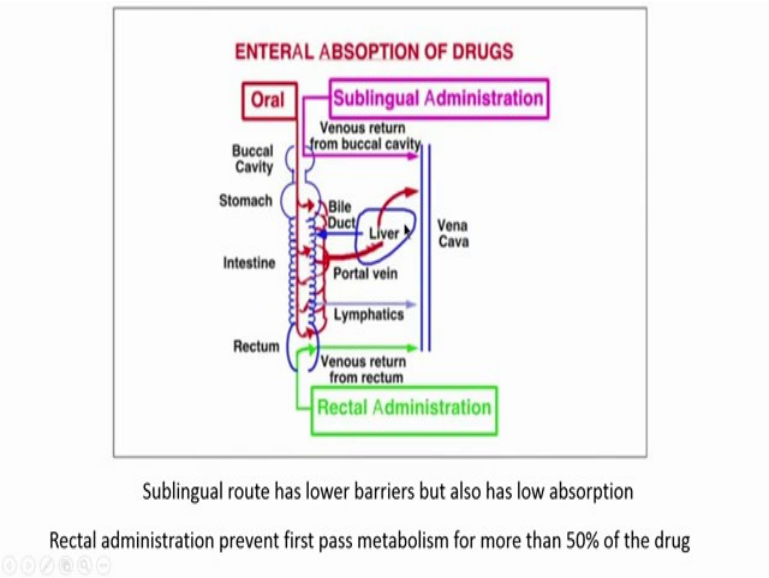

Of course, one thing that, I should mention is cells have their own mechanisms for taking up ionic molecules. So, they have channels and special proteins that carry the ions

throughout the membrane. So, again this is a pictorial representation of what happens, when you take a drug orally. So, eternal absorption essentially, mean absorption through the GI tract (gastrointestinal tract). So, there are several forms of absorption that can happen here. When you take a drug orally, first it goes to the buccal cavity, which is essentially nothing but, your mucosal surface in the mouth from there also the drugs can get absorbed. This is also called sublingual administration, but since the surface area here is low and most of the drug is immediately swallowed by us; most of the drug is passed into the stomach, the stomach again has a very low pH and lot of bile to digest the drugs.

From the stomach, the drug goes into the intestine, which is a very very large surface area and lot of absorption, that happens after you eat a food is through this intestinal absorption. From here, nearly all of the drug goes into the portal vein, which goes to the liver, which is again a detoxifying organ in our body, which can then clear any kind of harmful metabolites or metabolize whatever is foreign agent as well as any food particles and then, that goes back into the blood.

And finally, whatever is not absorbed in the intestine goes to the rectum. At rectum, it can either go out from the anus or the urine. There is also a big vein that goes through the rectum which can absorb a lot of fluid as well as a lot of molecules. So, a separate field has evolved for the rectal administration targeting this route so, absorption can happen in all of these places. So, again just to point out some things sublingual has low barriers; from here the drug directly goes into the buccal cavity; however, it is not very convenient for patient to keep the drug in the mouth for long durations. And so, the absorption is low as well because, first of all the residence time in that area is low and as well as the patients do not keep it there plus the whole surface area is not enough for the drug to go through.

And then we will talk about the first pass metabolism, but essentially, all the drug that goes to the liver, because liver is a detoxifying agent it gets metabolized quite a lot, but if you give it either by rectal or by sublingual, you avoid the passage of the drug through the liver, which is always good; if you do not want the drugs to get degraded. So, we will talk about this first pass metabolism in upcoming slides.

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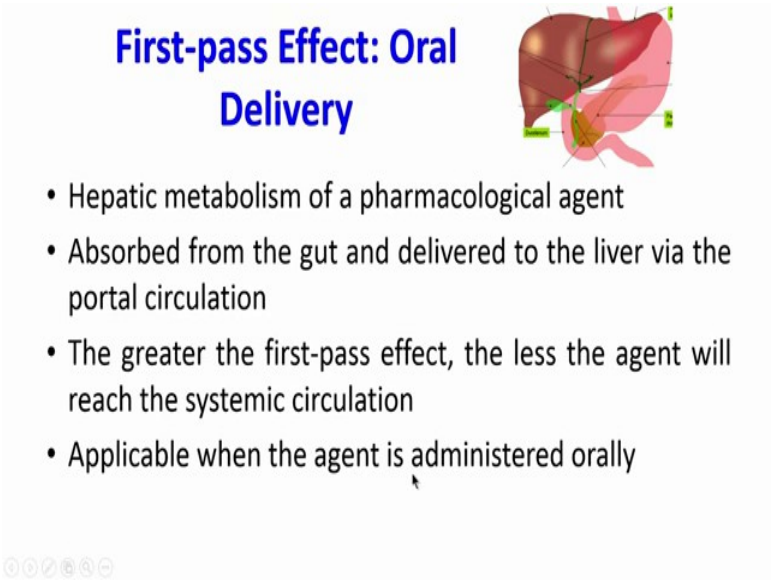

So, what is first pass effect? So, typically as I just said if you take anything orally, all of it that is absorbed through the intestine which is the majority of the drug will go to the hepatic metabolism essentially metabolism in the liver. Once these are absorbed through the gut and delivered to the liver through the portal circulation, the liver will degrade it and this is called the first pass effect. So that means, that even before the drug has reached your blood, there is a lot of drug it is degraded in the first pass itself through the liver.

And so, less of your agent is going to reach the systemic circulation and that will decrease that therapeutic efficacy, but this is only applicable, if you are administering something orally. If you give it via some other route, you may prevent the first pass effect.

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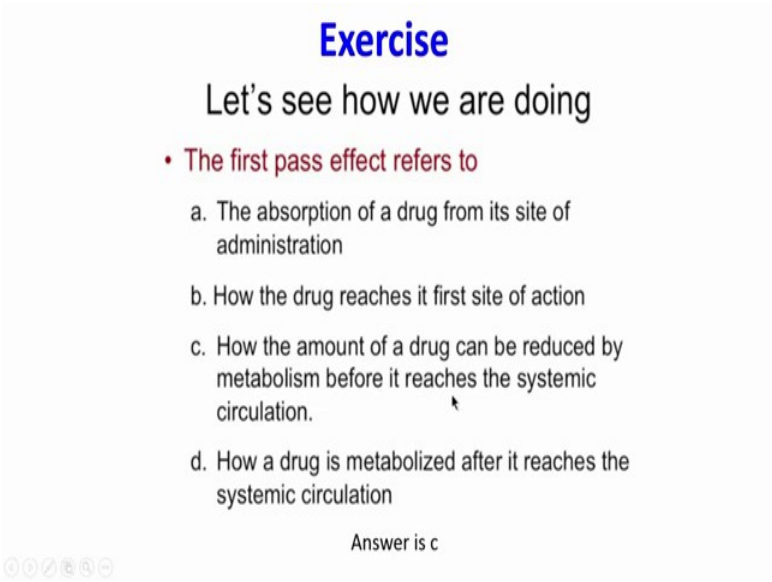

So, let us see how we are doing here? So, if I say the first pass effect refers to; is it the absorption of drug from the side of administration? Well not really, I mean if I give an IV injection or if I give some other route the first pass effect is not even involved. So, this cannot be correct. This is how the drug reaches its first site of action, again this is incorrect, if I give an intramuscular injection this thing is reaching immediately to the muscles, but there is no first pass effect involved here; is it how the drug is metabolized after it reaches the systemic circulation; again no this is before it reaches the systemic circulation.

So, it goes to the liver where it gets in metabolized. So, the answer is c, which is the how the amount of the drug can be reduced by metabolism, before it reaches the systemic circulation by the liver? So, the answer here is c.

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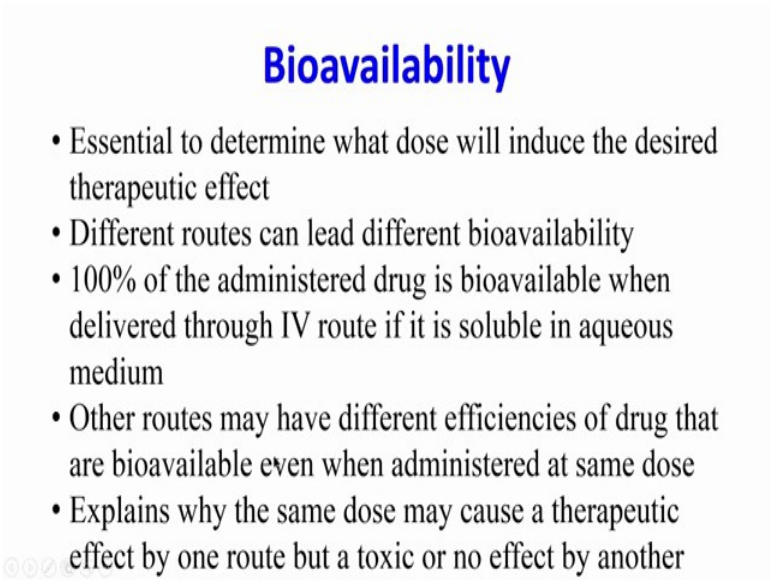

So, we will talk about bioavailability; again whatever you administer it needs to be bio available and what that means is, it is present in the body for the body to be able to feel the effects of the drug or for the drug to be able to go and do whatever it needs to do; bind to a receptor, change the pH or whatever it might be needed to do in the body.

So, different routes can lead to different bioavailability and it just said you can take things orally, but lot of it will first get degraded into the GI tract and then, also get metabolized during the first pass effect. So, not all of it is going to be available. However, if you do administered something through IV route and if it is completely soluble; then all the 100 percent of the drug that, you have administered is available.

So, again depending on the route you are using the bioavailability will change. The other routes may have different efficiencies of drug that are bioavailable, when administered the same dose. So, this explains why sometimes a drug may be toxic through a certain route, but may not be toxic through some other route. It is because the concentrations may change depending on what route you are using to take the drug.

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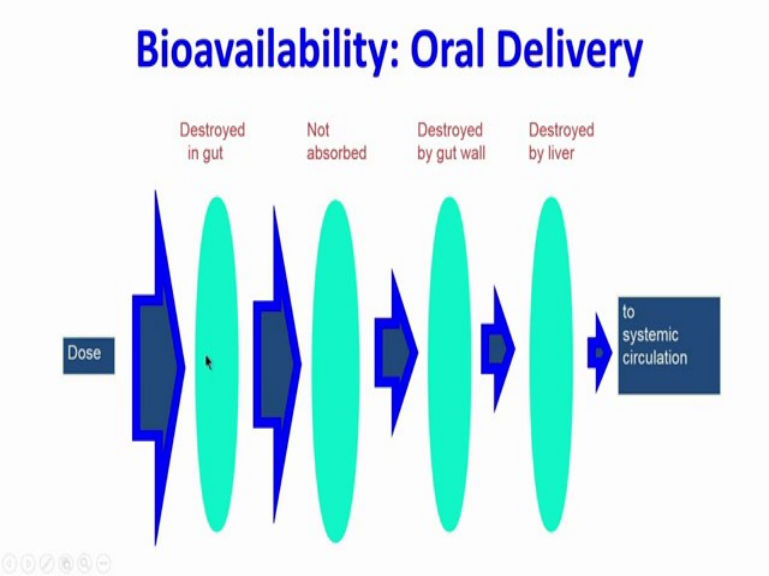

So, here is just a quick recap of oral delivery by availability. So, let us say you take a certain dose of drug most of it get destroyed in the gut itself; then, lot of it does not get absorbed and gets excreted out; whatever does get absorbed might not be able to pass through the gut membrane itself. So, lot of it gets stopped there and then whatever does reach through the hepatic portal vein its gets metabolized in the liver and only a small fraction of this.

So, you started with lot of drug here and only a small fraction of this is going to the systemic circulation. So, whatever now goes into the systemic circulation is essentially bio available.

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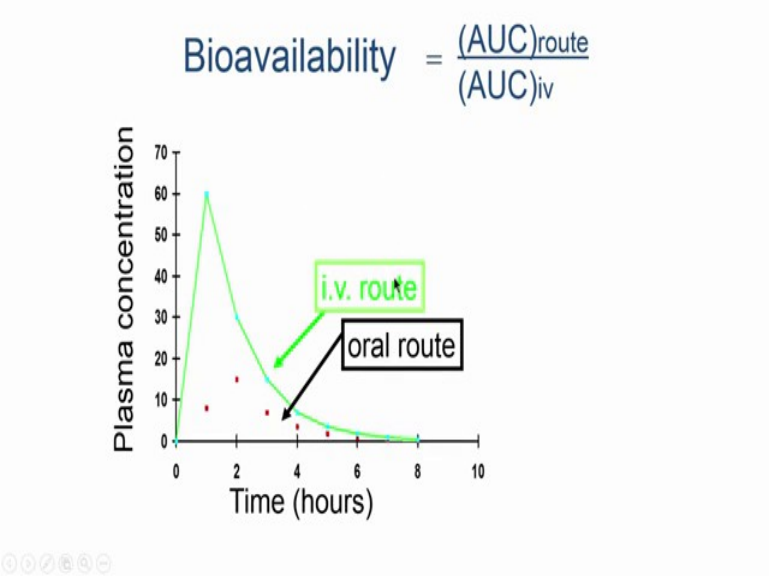

So, there is a parameter to define it, as I said if you inject something through IV route 100 percent of it is bio available. However, you can define a bioavailability of a route depending on what is the AUC, which is essentially area under the curve for a particular route. So, what do you mean by area under the curve?

So, let us say, this is the plasma concentration plotted against time and you have two different curves for different routes administration. So, let us say, if I give something orally at time 0, immediately is going to shoot up to a certain plasma concentration depending on how much of it we had given. And then, eventually it is going to start getting excreted or metabolized from the body; whereas, if I give the same amount of drug through some other route; in this case, let us say oral route; then, only a fraction of it is going to reach and then, it is going to get excreted out as well.

So, this area under the curve with the IV route versus the area under the curve with the oral route, will give you the bioavailability of the oral route. So, as I said bioavailability for the IV route is always going to be 1 or 100 percent in this case.

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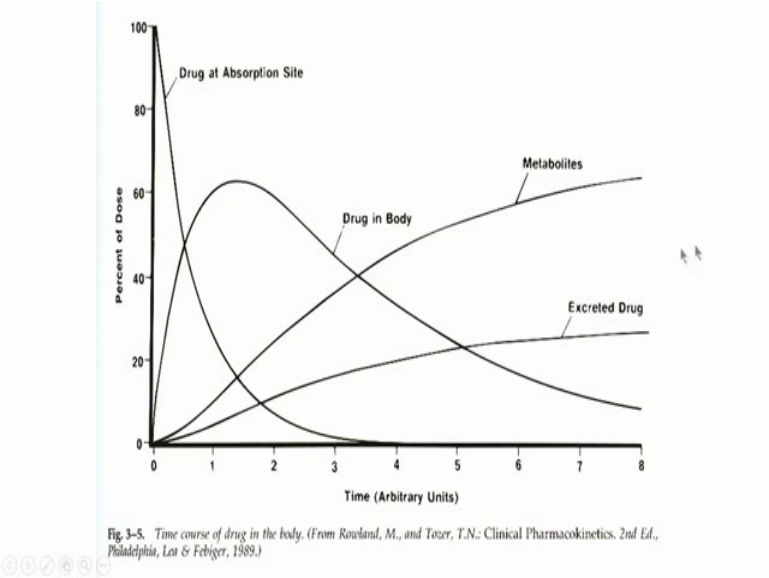

Fig. 3–5. *Time course of drug in the body. (From Rowland, M., and Tozer, T.N.: Clinical Pharmacokinetics. 2nd Ed., Philadelphia, Lea & Febiger, 1989.)*

And this is again just a pictorial representation of what happens to different compartments of the drug? So, you give a drug at a certain site; let us say I do a subcutaneous injection.

So, at the site at that, point of time this 100 percent of the drug this could be subcutaneous this could be intramuscular or this could be even IV route. So, I injected into a vein at time t equal to 0; there is a lot of drug at the particular vein that, I injected it in; over time what will happen? Is the drug will start to diffuse and absorbed through the system? So, this drug concentration the absorb site will decrease and of course, these are arbitrary units. So, this could be seconds milliseconds hours just depends on what route you are choosing and it will eventually get excreted out. Whereas, as this is going down the drug in the body is increasing because, from the site it is getting diffused into the body. So, the drug in the body increases for a certain time and then the body starts to metabolize, starts to excrete it. So, then it eventually starts to go down.

The metabolites of the drug; we will start to increase as the concentration in the body is increasing and then, will continue to increase as more and more drug from the body gets metabolized and at a certain point reach a steady state and eventually, will start to fall out, when these metabolites get excreted and then, some of the part of the drug will also get excreted out, again also depending on the concentration of the drug present in the body at the time.

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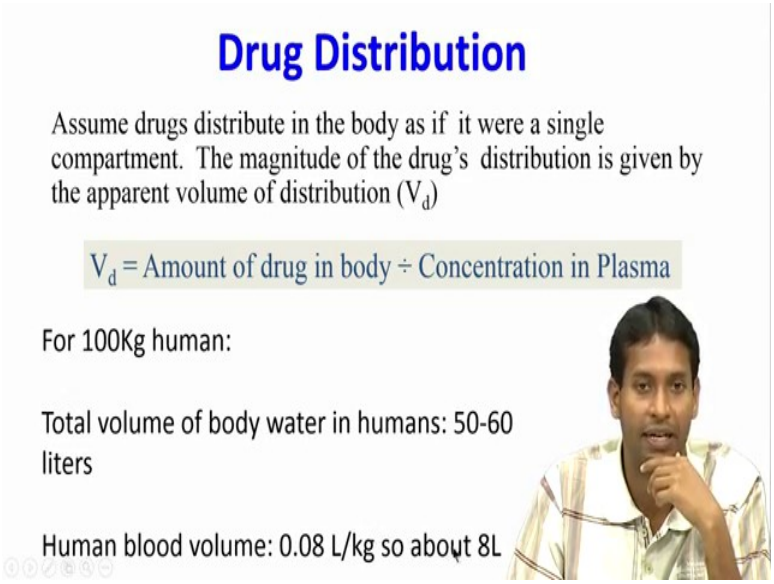

So, how do we study this drug distribution? How do we know that how much of the drug is in the plasma available throughout the body versus how much of the drug is present in the whole body? So, may have diffuse out from the plasma of different tissues. To do that, we have a term which we define as Vd.

$$V_d = \text{Amount of drug in body} \div \text{Concentration in Plasma}$$

So, this is called the apparent volume of distribution. This is just an arbitrary value this has no physical meaning, but it is a value that, helps doctors and engineers to kind of understand how the drug get distributed in the body and where it is compartmentalized.

So, let us do a quick exercise. So, let us say for a 100 kg human; we know that the volume in the body for the water is about 50 to 60 liters and then, the total blood is about 8 liters. So, if we assume that, lets do a quick example.

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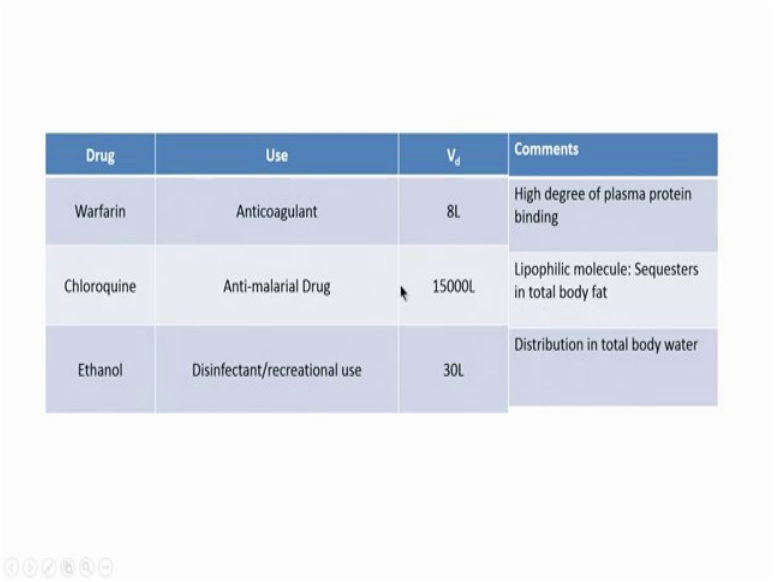

So, I have these three drugs, these are actual values. So, this warfarin chloroquine and ethanol and I have listed the uses here; one is anticoagulant, another is anti malarial drug, another is disinfectant. So, let us talk about warfarin first. If I say, the Vd is 8 liter what does that mean? So, does it mean that, the apparent volume distribution is 8 liter, which means that, the concentration? So, what was Vd again? It was concentration of the drug in the body divided by the concentration in the plasma. Actually, amount of drug in the body divided by the concentration in the plasma.

So, if I say its 8 liter; that means that we are saying that all the warfarin, that we have given is distributed within the 8 liter volume and this is very close to the volume, I said the total volume of the blood in the humans so; that means that, we can predict of course, these values may not be direct indication, but we can with fairly well confident say, that most of the drug is distributed in the blood itself; it compartmentalizes itself in the blood it is not able to diffuse out of the blood. Let us talk about chloroquine.

So, this we are saying is an anti malarial drug and has a Vd of 15000 liters. So, what does that mean? That means that, it is distributed quite a lot. So, if we go back to the formula it means that, the amount of the drug divided by the concentration in the plasma. So, if this is very high; that means that, the amount in the plasma should be very very low to get this value to be that high, because this is not the volume of our body.

So, the concentration the plasma has to be very very low to get to this value. So, what this means is that, the drug is definitely not localizing in the plasma; has a very very low localization in the plasma, which may mean that the drug may not be very well soluble in water.

And so, it is mainly compartmentalizing itself in lipid components in the body. So, this is the inference we can draw from here and then finally, ethanol again is used as recreational or disinfectant use and we find that, the Vd is about 30 liters, which is again close to the total body water. So that means, that the ethanol gets distributed throughout the body in the water areas and unlike warfarin which was localized only in the blood it is able to diffuse through the body.

So, let us see, what we get. So, as we said, warfarin has a high degree of plasma protein binding. So, it binds to plasma protein and because, it is bonded to a protein, which is big it stays in the blood; whereas, in case of chloroquine, it is a lipophilic molecule. So, it is sequested in the total body fat as is indicated by the Vd and finally, ethanol which again distributes in the total body water. So, and this is all we have for this lecture; we will continue with the pharmacokinetics and talk more about elimination and how things are excreted from the body in the next lecture.

Thank you.