Computer Aided Drug Design
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Lecture - 09
ADME

Hello everyone, welcome to the course on computer-aided drug design. We will start a new topic that is called ADME. A stands for absorption, D stands for distribution, M stands for metabolism, E stands for excretion that means absorption into the plasma, distribution inside the plasma and tissues, M is the metabolism that is taking place in the liver. And because of the presence of different enzymes E is the excretion that is throwing out from the body either through the various urine or through the inhalation and exhalation okay.

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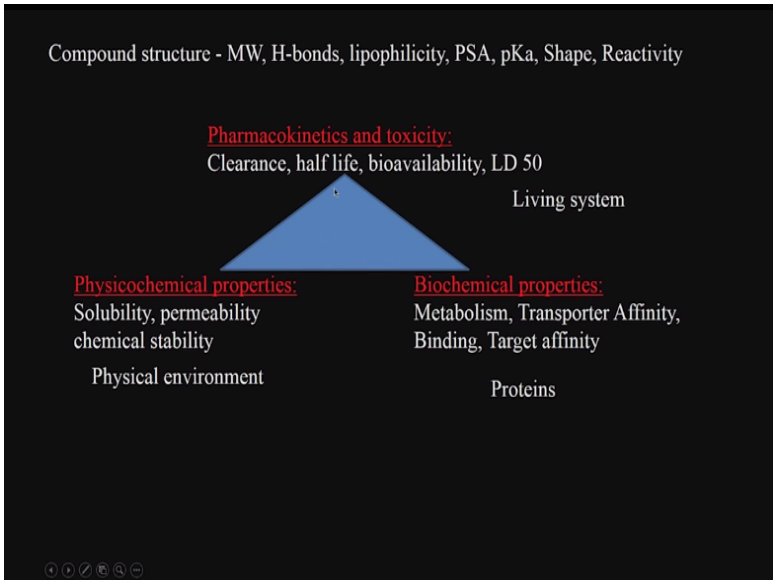

So I did show this in the previous class so we have the compound structure, which we can play around with molecular weight, hydrogen bond donor, acceptor, the lipophilicity or the hydrophilicity, the polar surface area, the pKa, shape and which affects the reactivity. Now 3 things are connected with each other, the physicochemical properties that means solubility, permeability, chemical stability okay.

And the pharmacokinetics and toxicity that means the clearance from the system, the half-life, the bioavailability, the lethal dose that is with respect to the living system and here with respect to the proteins, the metabolism, the transporter affinity, binding to protein, target

affinity, so all these are interrelated okay so we can change a few parameters or structural features or descriptors.

But in the physical level they get modified, in the biochemical level they get modified and in the living system also they get modified okay.

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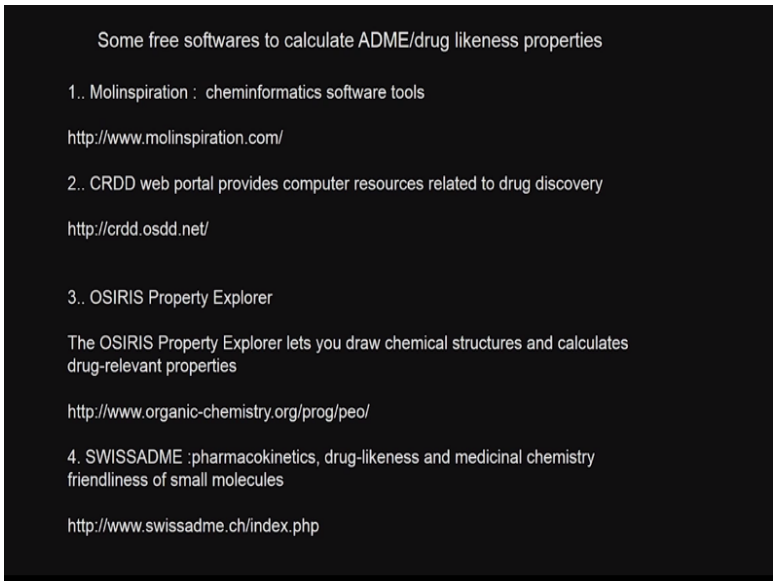

There are lot of free softwares, one is called Molinspiration, then the CRDD web portal that is computer resource related to drug discovery, OSIRIS Property Explorer, SwissADME, all these softwares can try to predict many of these properties like solubility, metabolism and the various ADME properties, stability and so on. For example, if you take this first one the Molinspiration.

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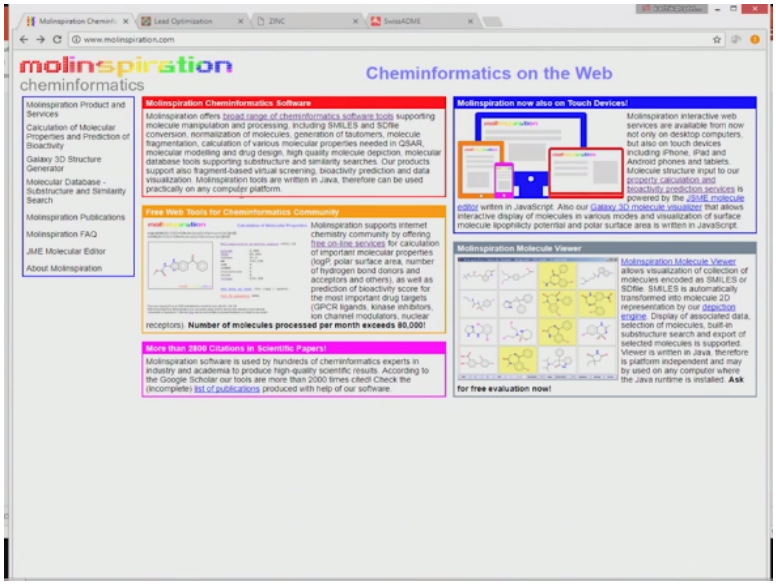

That is quite interesting software so this is called the Molinspiration software okay so we can go into free online services. We can draw structures here. We can draw any structures or if I have the smile notation I can download. For example, if I have metformin I can download or I can draw a structure, here I will show you metformin if I search okay so this is metformin.

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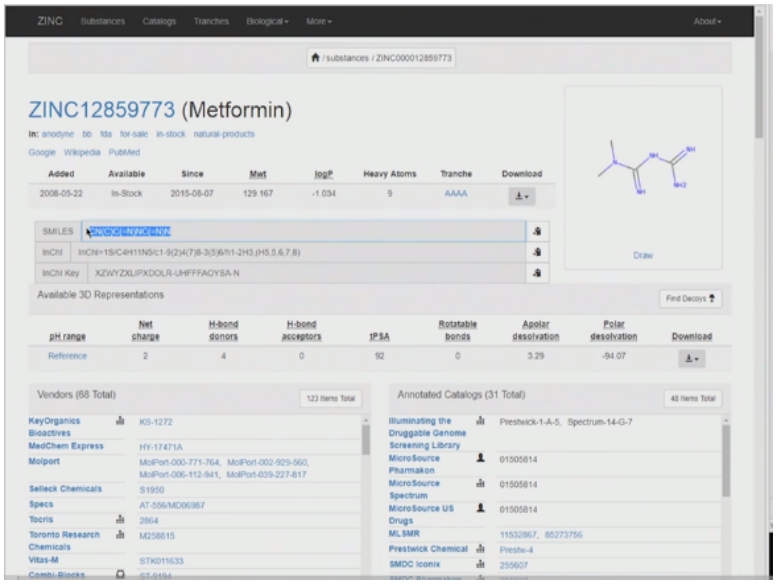

Yeah we can copy the smiles notation okay and then take it to the Molins and then we can enter the smiles notation okay, so metformin is taken here and it gives you lot of properties. Log P this is based on some software, total polar surface area, number of atoms, molecular weight, number of nitrogen, OH, NH. Does it violate certain rules, rotatable bonds, so it has got 3 rotatable bonds as you can see here 1, 2, 3, volume of this molecule okay.

So this is the molecule, it is copied from the smiles, I can predict the bioactivity of this molecule okay. So does it bind to a G-protein receptor, iron channel modulator, does it kinase inhibition activity, nuclear receptor ligand, protease inhibition, enzyme inhibition, so it can do all those things okay.

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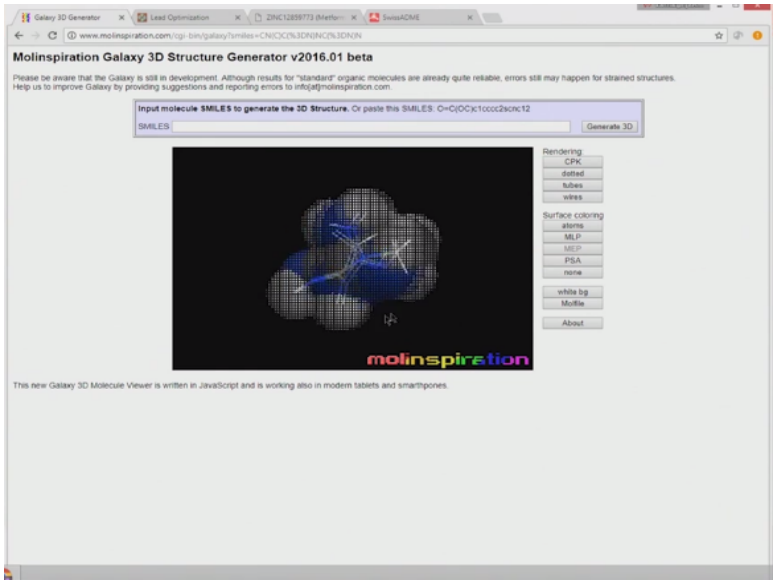

Then we can even draw 3-dimensional structure of this molecule as you can see we can view it and we can get the polar surface area. Polar surface area leads to nitrogen right. So all the nitrogen's will appear polar as you can see here okay. This is the electrostatic potential on this okay and then we can put in a dotted form so it gives you dotted form or it could be in a tube form so you can look at the molecule in the tube form, it can be wire form, this is the standard okay.

So we can do all those things or so from the zinc we can copy, we can get properties or we can draw molecule of our interest as medicinal chemist I feel that I would like to synthesize a molecule like this okay.

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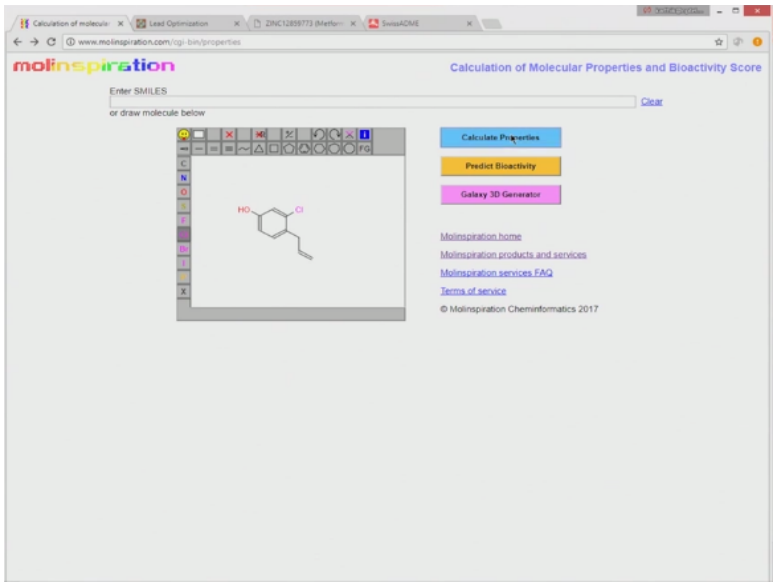

And I want to know the properties of this molecule okay so I want to put another here then I put a chlorine just blindly I am putting something so we can calculate properties of this molecule so it gives you Log P 2.89 so it is neither too much hydrophobic or too much hydrophilic which is good. Total polar surface area is low because it is predominantly lot of CH2, carbons that is why polarity is very low okay.

Solubility maybe a problem, number of atoms, molecular weight, it is giving all these details okay. We can look at the bioactivity of this molecule. See it gives you all this bioactivity.

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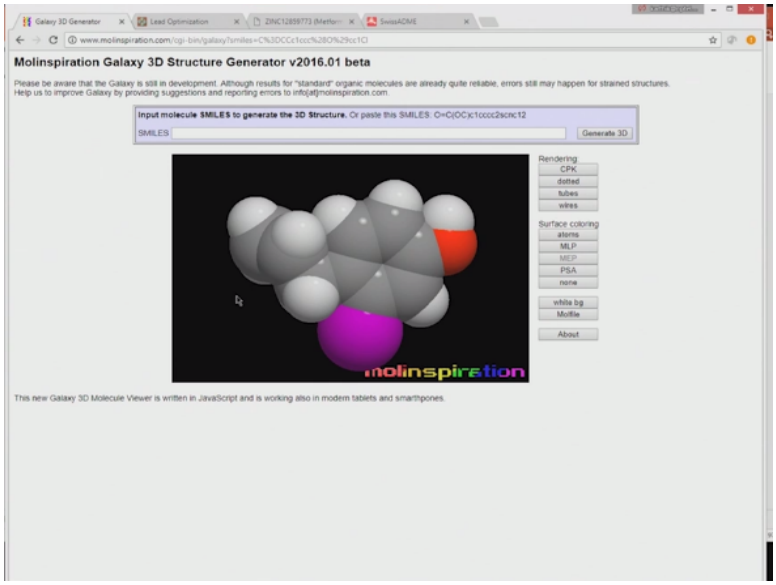

We can draw the 3-dimensional structure of this and look at how it looks like okay, molecule and then we can look at polar surface area. As you can see only very little polar surface area okay because of the presence of oxygen, so predominantly it is a highly hydrophobic system okay. So this is a very interesting Molinspiration as it is called we can do that.

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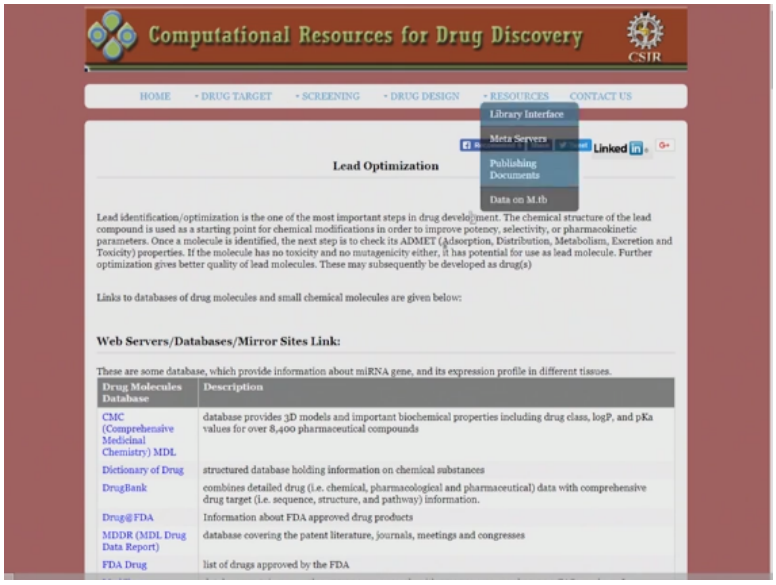

Another software like I mentioned CRDD web portal we can look at that also that is called computational resource for drug discovery. There are lot of softwares which can do the predictions okay as you can see here, will not go too much into this. The third one which is the OSIRIS Property Explorer and again will not go into that also okay. If you want to look at that front page this is called OSIRIS Property Explorer.

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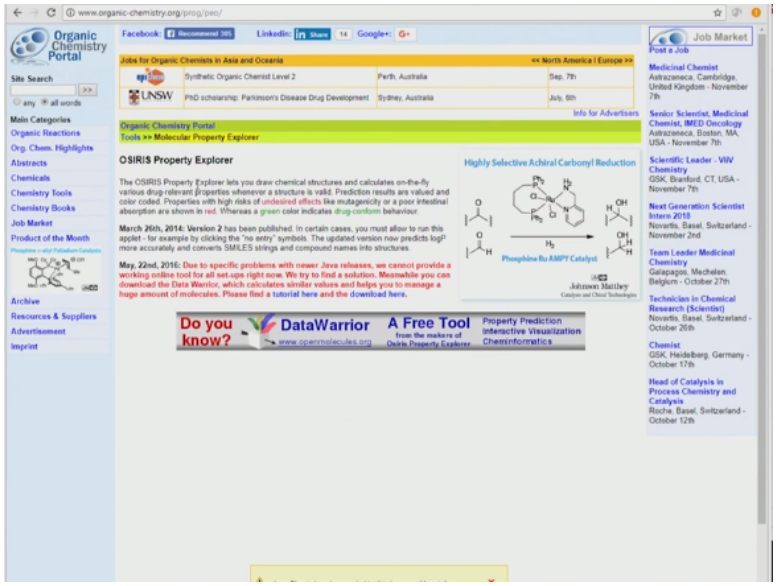

Yeah this is OSIRIS Property Explorer. As you can see again we can look at many properties, tools, molecular property tools as you can see here we can get the property tool. We can try to get molecular weight, fragment based design, prediction, solubilities, all those things can be done.

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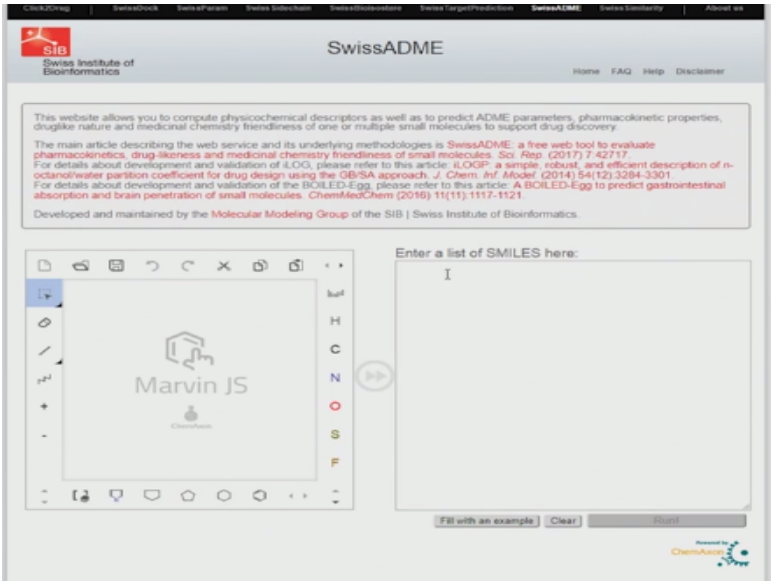

Of course, SwissADME is also there. We can use the SwissADME and then try to get property. For example, metformin, we went to metformin right so we can put the metformin, go to SwissADME, enter the smiles notation here and then we can run so SwissADME gives lot of information as you can see and still working.

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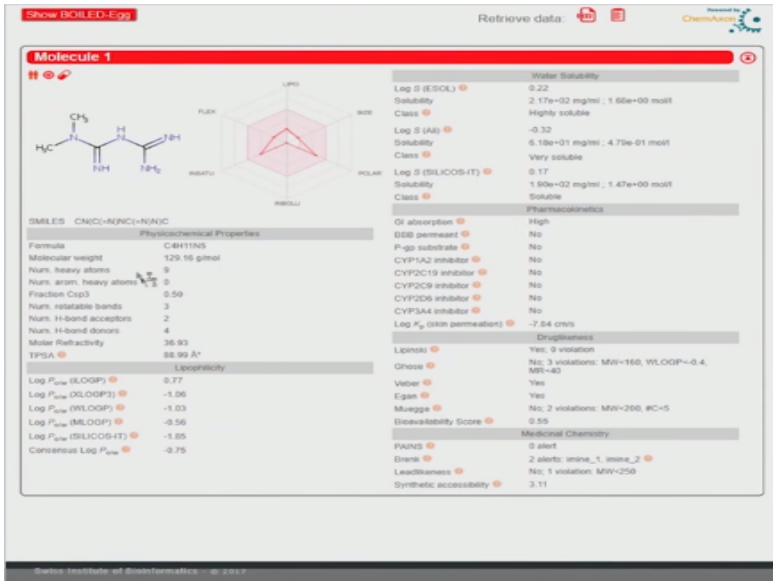

And it gives you molecular weight, number of atoms, it gives you Log P in different, different techniques, different types of softwares, measures Log P in different ways. So it gives you an average or consensus Log P in the bottom, it gives you total polar surface area, molecular refractivity, hydrogen bond donors, hydrogen bond acceptors, molecular weight and GI absorption, then blood brain barrier, then PGP that is P-glycoprotein.

Does it act as a substrate for that? No. It gives you solubility data here. Some of these rules we will talk about later and this also PAINS we will talk about later okay. So it gives you lot of properties cytochrome-P, does it go and inhibit that and so on actually okay and then bioavailability also must be there somewhere, bioavailability 0.55 that means that is good, of course metformin is a drug okay.

So this is also an interesting graph, which puts in the lipophilicity size, flexibility and number of unsaturated and then saturated that is because of and then it draws the molecule or if it falls within this pink that means it satisfies all condition. If one of the properties falls outside so you may have a structure which looks different. So the SwissADME is also good software for predicting lot of properties, Molinspiration.

So all these softwares are good for calculating properties. As we go long, we will see more of that okay.

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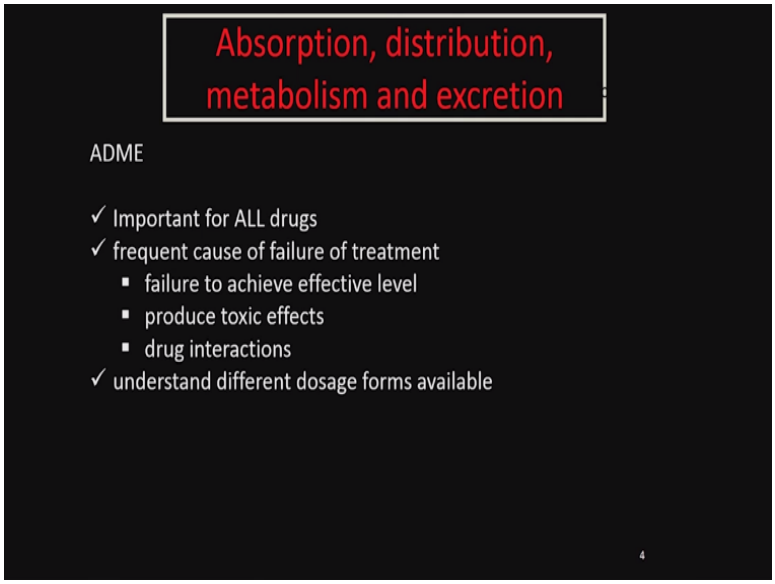

So what is this absorption, distribution, metabolism, excretion? So we are going to spend lot of time on them. This is important for all drugs. Its frequent causes are failure of treatment frequent because you are not getting effective level. If I am having a bacterial infection, my concentration of the drug at the infected site should be higher than the minimum inhibitory concentration of that bacteria.

So that the bacteria get killed okay so that is called the effective level or it may produce toxicity, sometimes the drug maybe too much, concentration maybe too much, it may be

producing toxicity drug-drug interaction. If they have 2 drugs, 3 drugs given to the same patient, for example for blood pressure they may give you a beta-blocker and they may give you ACE inhibitor and they may also give aspirin for blood thinning.

So you have 3 drugs, there could be interactions between these drugs. We want to understand different dosage forms, sometimes the drug is given orally, sometimes intravenous, intraperitoneal, intramuscular, intravaginal, it could be through the skin, it could be nasal. So we need to understand how the drug gets into the plasma through different routes. What happens to the maximum concentration and so on actually okay?

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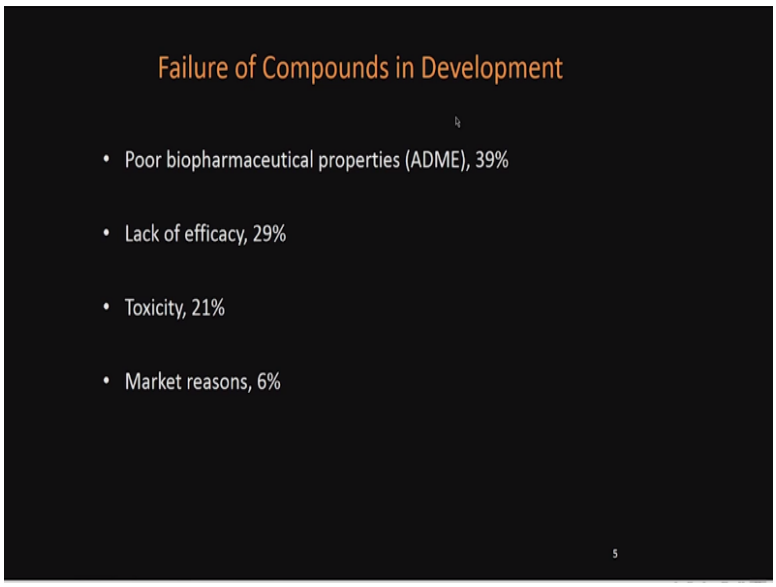

So we need to understand ADME which is very important and most as you can see 39% of the drug failure during clinical trials because of poor ADME. We realize that when we do animal trials and when we do human voluntary trial. Lack of efficacy, the concentration at the target side is not sufficient and if there is a tumor the concentration of the cancer drug should be high enough to kill the tumorous cells okay.

Toxicity, 21% of the drug fails because of toxicity so you see we need to address that which is based on as I have been telling the bioavailability, how it gets absorbed in the GI, the solubility, the lipophilicity, distribution inside the blood stream whether it gets metabolized because of the presence of different types of enzymes, does it get metabolized because of different pH conditions, does it get excreted even that is very important okay. So we will look at each one of them.

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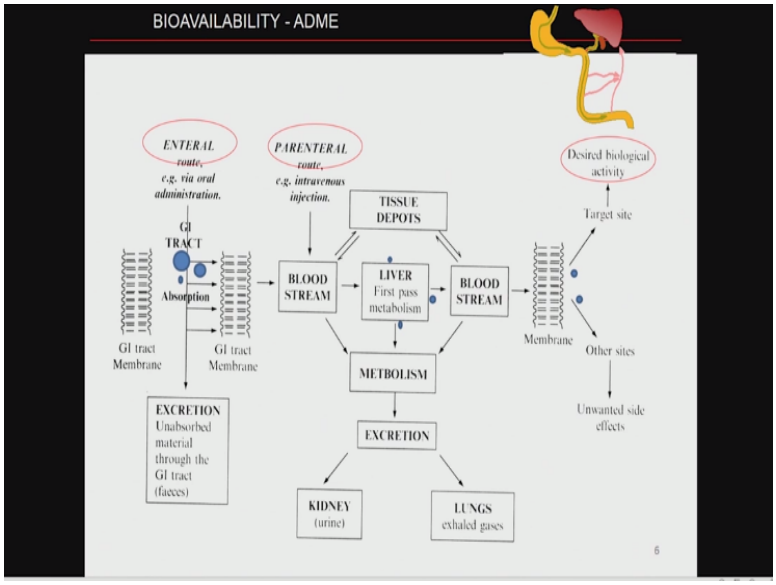

So this is how the drug travels, so imagine I given a drug orally okay, a tablet form okay, so the drug is given as a tablet form, so it goes into the GI tract, it goes through the stomach, the pH is 1 to 2, then it goes to the small intestine, finally to large intestine that is colon okay. So the pH keeps increasing coming to basic so drug solubility becomes a problem, drug dissociation happens and drug gets absorbed okay.

So if it does not get absorbed, drugs get excreted okay so some portion is lost. So it gets absorbed, it comes into the blood stream and then liver is the fantastic gatekeeper so it starts degrading the drug. So if it gets degraded and some drug gets absorbed in the tissues okay, some drug gest degraded, metabolism, excretion, kidney, lungs so you lose, some drug gets attached to the tissues absorbed so you lose.

So only small amount of drug goes into the blood stream and goes reaches the target site and again only part of the drug will go to the active site part of the drug will go and bind to other proteins so that also becomes useless. So only a small amount reaches the target site. So I may be given a large concentration of the drug but what reaches at the target site maybe very less and this ratio is called the bioavailability.

So maybe 20%, 30%, 40% and higher the percentage better because I can give a small quantity of the drug so toxicity is low and I do not have to frequently give the patient the drug so bioavailability larger the value better it is and as we saw in SwissADME software we approximately get a feel of the bioavailability. Metformin it gave a number of 55% okay. So

if you go to the data base like drugs.com okay it may give the actual value because metformin is a real drug okay so this is called the bioavailability.

This determines the drug dosage, this determines even toxicity because if the bioavailability is poor, the patient has to be given large quantities of the drug so that it could be toxic. If the bioavailability is very good, patient has to be given smaller quantity. If too much drugs gets excreted that means if the half-life is very short so the patient has to be given frequently the drug that means the dosing times increases.

So everything is determined by this particular picture okay. This picture gives you nicely what is happening at different places as the drug travels right from the oral cavity in the mouth right up to the target site okay.

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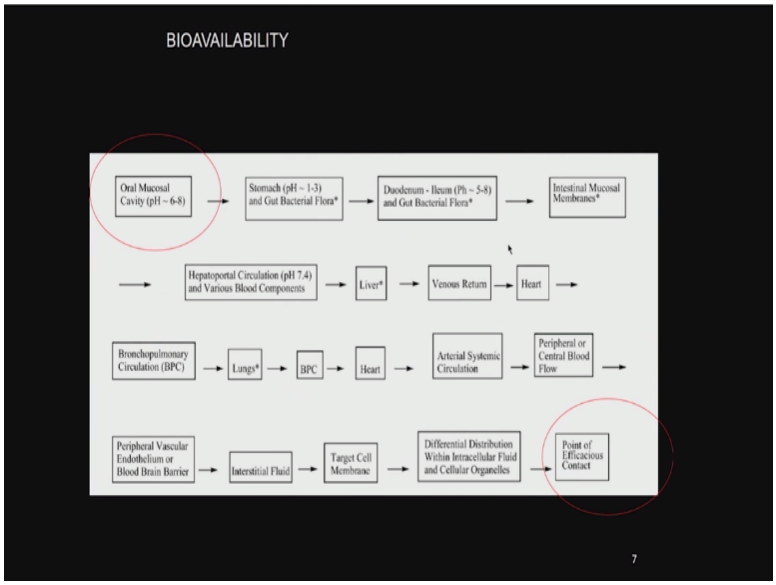

Now another thing that happens is the drug when it comes to the oral mucous cavity pH is 6.85 but as soon as it reaches the stomach the pH as I said is very low 1, 2, 3, so that means there could be a drug degradation because of acidic pH. For example, ester bonds can break because of acidic pH, amide bonds can break because of acidic pH, so we need to watch out. Then when we come to duodenum, ileum and so on, the pH goes up and up so it goes to 5 to 8.

When the drug goes to the plasma region, the pH is 7.4 okay so the drug stability, solubility, everything should be constant irrespective of the changes in the pH. Then, it goes to the liver where there is lot of degradation, then it goes to heart, then circulation system, lungs, arterial

system and so on okay. Then it goes to the target cell membrane then it has to get into the target site and becomes efficacious.

So there is a distribution of the drug and it is like a big pot of water where you put small amount of salt. When the salt gets totally distributed concentration becomes low. If the amount of water in the pot is very large, concentration becomes very small. If the amount of water in the pot is very small, concentration is high. So the volume depends not only on whether it is male or female.

But also on the type of drug because some drugs will remain only in the blood stream, some drugs will also get absorbed in the tissues so the concentration in the blood stream becomes low. So it depends on the type of drugs okay. A very small molecule can easily get absorbed in the tissues, so the amount present in the blood stream maybe low whereas a large molecule and hydrophilic may not get absorbed so the concentration in the blood stream maybe very high.

So for the same person depending upon the drug, the volume of distribution as we call it can change okay so it is not constant. So it can depend on the (()) (18:48), it can depend on the gender, it can depend on the type of drug, it can even depend on the food we eat and the health of the patient and so on actually okay.

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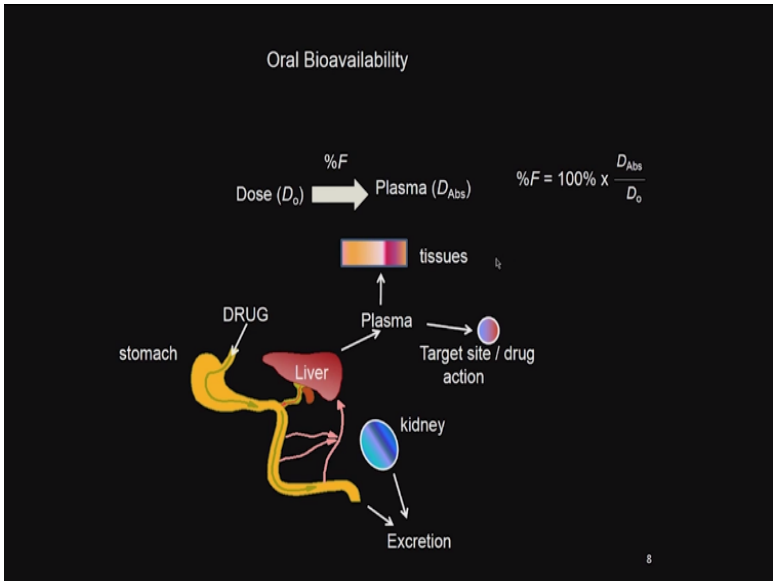

So as I mentioned the drug comes in and travels, it gets absorbed into the liver and whatever is not absorbed goes as excretion, from kidney also there is excretion. From the liver it goes

to plasma, it gets absorbed in tissues and finally reaches target site so this concentration that was the ratio multiplied behind this is called the oral bioavailability and it is mentioned as F okay that is the oral bioavailability. This is a very important parameter to understand okay.

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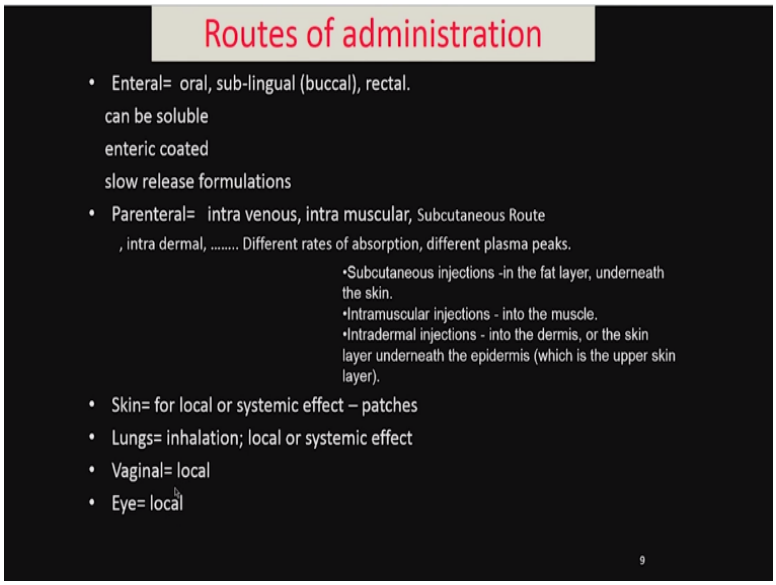

So when we talk about absorption, there are many routes for administration of the drug already so it can be oral, sub-lingual, rectal, so it can be soluble form okay, it could be enteric coated so the coating goes away because it keeps the drug stable without degradation or it could be a slow release formulation. There are now slow release partially crystalized metformin are there.

So it could be a slow release formulation so the drug gets to over a period of time okay. Parenteral, it could be intravenous, it could be intramuscular, it could be subcutaneous, intradermal, so different rates of absorption you are going to have, different plasma peaks so if I introduce the drug orally after about 1 hour, 2 hours slowly the drug reaches the max.

And then it starts falling down whereas if I give it intravenously immediately you find a big increase in the concentration in the blood stream okay. Depending upon the route, the time at which the max happens changes and the amount concentration also will change okay. Skin, sometime skin patches, nicotine patches we have heard of right so all these matters. Lungs through inhalation like some bronchial drugs local or systemic effect like even some anesthesia okay through lungs.

Vaginal that again it becomes local okay, treatment of certain bacterial infection or fungal infection. So what is this subcutaneous means? That is in the fat layer underneath the skin okay and intramuscular means into the muscle, intradermal means into the dermis of the skin layer underneath the epidermis okay. So epidermis is upper skin layer so subcutaneous is into the fat layer whereas intradermal just below, intramuscular into the muscle region.

So you can have different types of parenteral routes. Of course, eye as you have got eye drops, they are again local okay. So some of them are local, some of them could be systemic okay.

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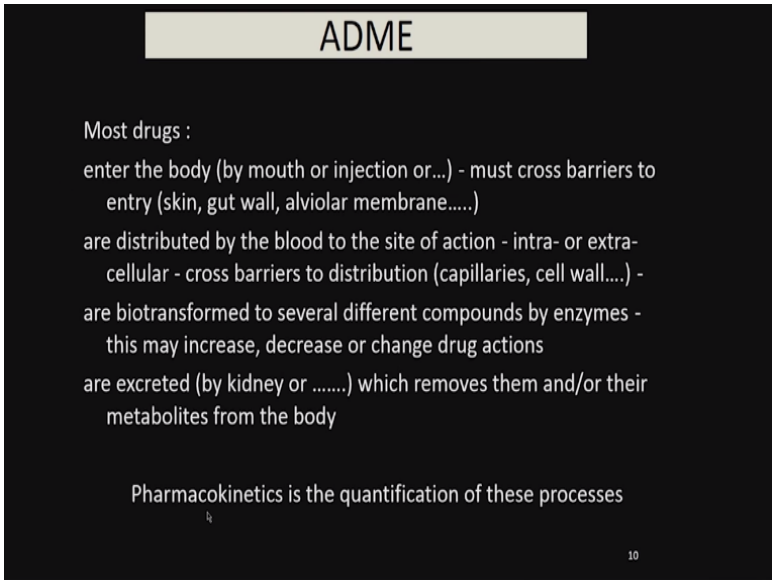

Most drugs enter the body by mouth or injection, they much cross barriers to entry that is skin, gut wall, alveolar membrane, then they get distributed by the blood to the site of action intra or extracellular, they have to cross the barriers so they may have to go through capillary, cell wall. They get bio-transformed to several different compounds because there are lot of enzymes in the liver.

Liver is a very fantastic gatekeeper, it starts degrading whatever compound is present, so you have esterases, hydrolases, you have oxidoreductases, you have lipases. So all these start degrading your material and your component may become either sometimes toxic or they may become totally useless inactive form or excreted so it can be excreted through kidney, different routes which removes them and/or their metabolites from the body.

So not only the drug even the metabolites may be getting removed. So pharmacokinetics is the quantification of the whole thing. So what the body does to the drug is called the pharmacokinetics okay and what the drug does to the body is called pharmacodynamics okay so one is called pharmacokinetics and one is called pharmacodynamics okay.

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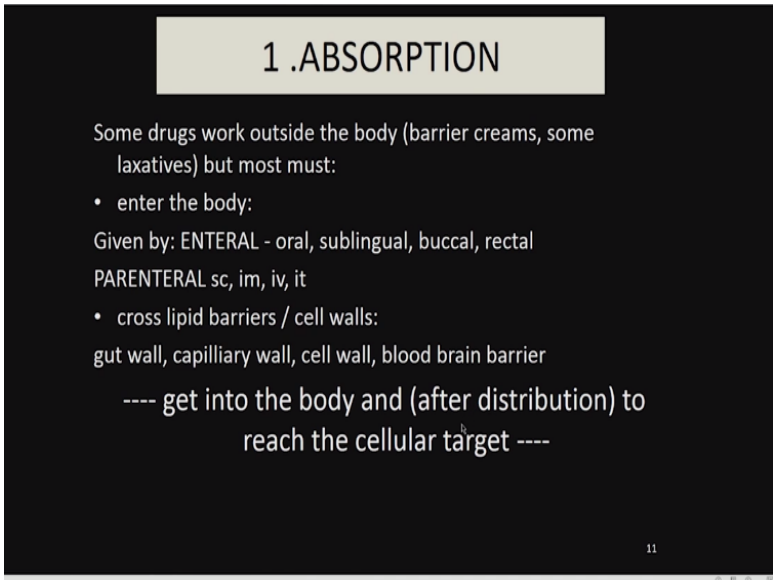

Let us look at each one of them little bit. Absorption, some drugs work outside the body like your creams, laxatives okay but even some antibacterial, fungal at the surface, some enter the body enteral, oral sub-lingual and so on. Parenteral okay subcutaneous, intramuscular, intravenous, they have to cross the lipid barriers and cell walls, gut walls, capillary walls, blood brain barrier okay. So lot of diffusion limitations happen. Then, they get into the body after distribution to reach their target okay.

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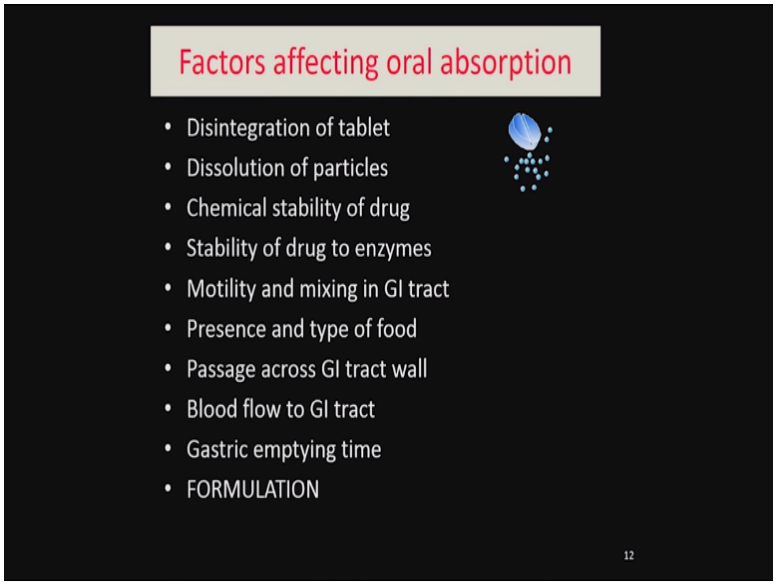

So what are the factors that affect oral absorption? Drug has to disintegrate that means the tablet if it is in a tablet form it should break down, it should completely dissolve that is dissolution. Drug has to be stable in that pH in the GI system, stability of drug to enzymes. There are so many enzymes which I mentioned about, motility and mixing in GI tract, they are mobile or they get mixed with the GI fluid.

They may be getting mixed with food and so on okay, presence and types of food, what type of food we have eaten, sometimes protein material can just absorb drug active ingredients okay. The drug may get diluted because of presence of fluids inside the GI, passage across GI tract wall that means through the passive diffusion so that means the permeability has to be reasonably good which we talked about in the previous classes okay.

Then blood flow to GI tract so depends on there is good blood flow in the GI tract. Gastric emptying time because again I showed you in the previous class the emptying time varies for example in the stomach it could be about only 3 hours max whereas if the small intestine it may go to several, several hours and then large intestine it could go into several days so the emptying time matters.

Formulation, how we have formulated the drug, the manufacturers formulated. He might have added surfactants, stabilizers, solubilizers so how it has been formulated?

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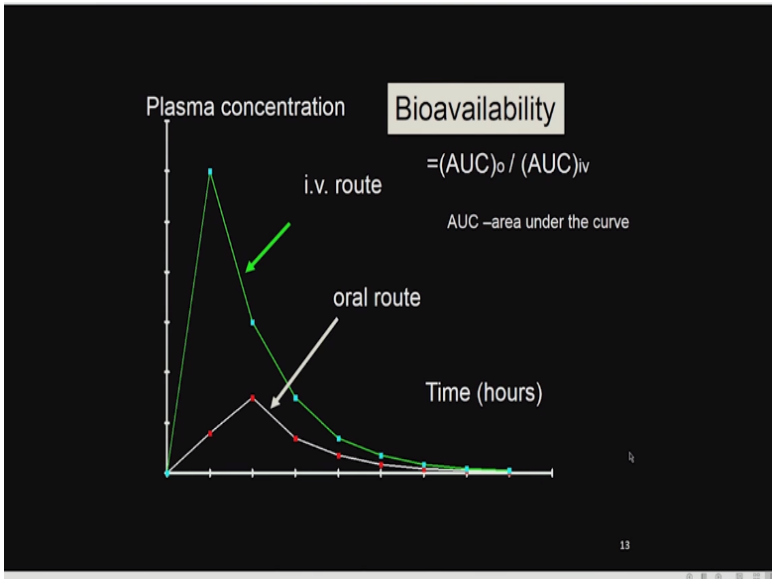

So all these matters so typically you can look at if the drug is given as an IV, the concentration of this drug will increase with time and then fall down. This y axis is

concentration; x axis could be time. If it is given orally, you will not reach that peak concentration and also the peak will happen much later because the drug has to solubilize in the stomach, get pass the permeable barrier, lipid barrier and reach.

So the max time will change and the level height also will change okay. So the bioavailability is area under this curve AUC oral/area under this curve IV okay. So obviously AUC oral will always be less when compared to AUC IV. So it will always be <1 so we can multiply by 100 and that gives you the F value or the bioavailability value. So that is how you can find out if I have a rat and the drug, I give it through IV, I get this particular graph then I mix it with this food and allow the rat to consume it orally.

And I will monitor the concentration of the drug as the function of time by taking blood samples and then I will get this graph, I take this ratio to understand the bioavailability of the drug okay.

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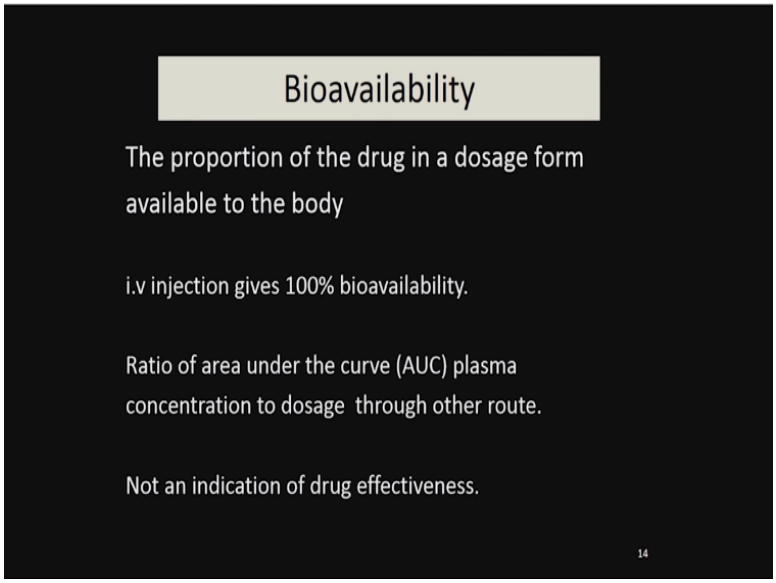

So bioavailability, absorption determines the proportion of the drug in the dosage form available to the body. Generally, IV injections we assume it gives 100% bioavailability. So it is the ratio of the area under the curve okay concentration through other route but it is not an indication of the drug effectiveness. It is only availability please remember it is not about the effect whether the drug is effective that is either it kills bacteria or either it kills cancerous cells that you might have collected data in your in vitro studies okay.

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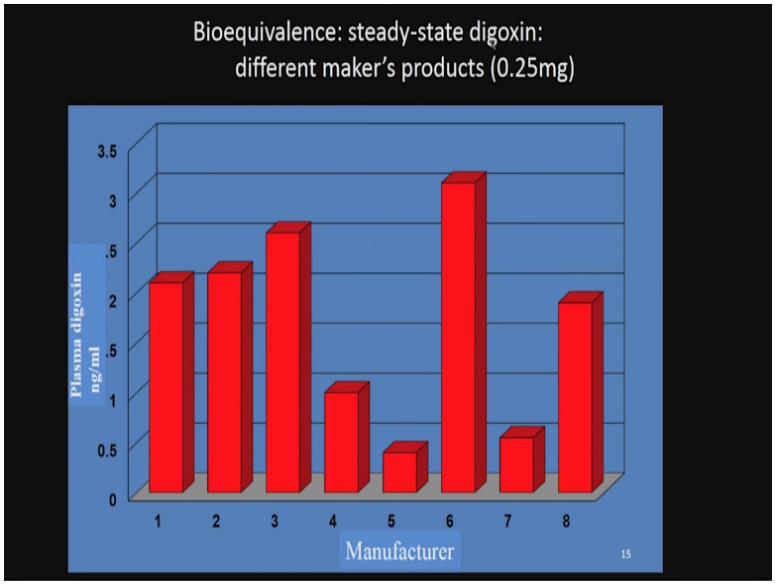

So the bioequivalence can change okay bioavailability or bioequivalence. For example, this is a very interesting data. This is a compound called digoxin okay and different manufacturers make this, imagine 8 different manufacturers make it and you give 0.25 milligram of that particular drug but the plasma digoxin concentration could be very different okay so much different as you can see here the mg/ml this manufacturer may have 3 whereas this manufacturer it could be 0.4.

So almost 10 times difference okay so the availability of this particular drug depending upon the manufactures change so much, why is it? Because of the way they manufacture, the way they make the tablet, the way these other components have been added, so it can change dramatically okay.

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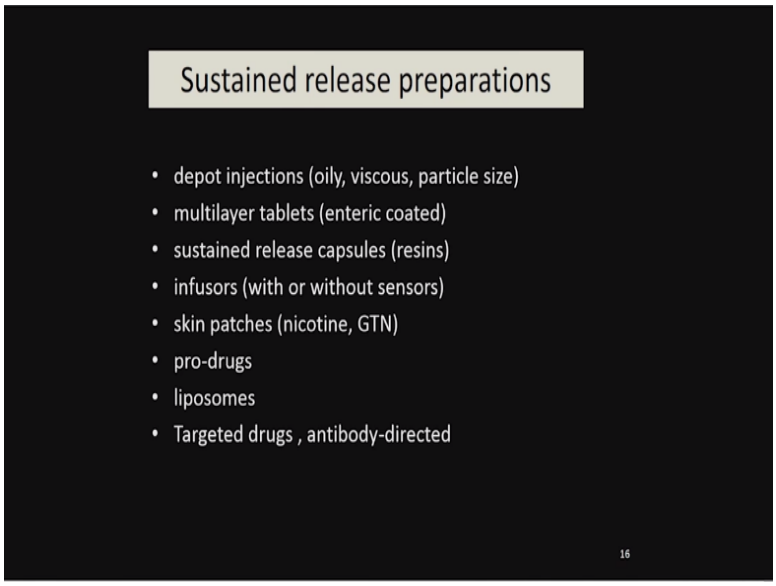

So sustained release preparations okay like with oil, drugs are mixed with oil or made into viscous material or made into particles so that it slowly degrades particles and releases the drug or viscous material. So the drug slowly comes out of this viscous oily material or multilayer tablets, we can have coating of different biodegradable polymers okay like gelatin, chitin and so on so they degrade slowly drug gets released slowly.

Multilayered tablets, it can help in slow release, it can reduce the toxicity, it can also help in the drug stability okay yeah. Sustained release capsules, so we can have it in resins, it slowly releases over a very long time. Infusors okay so the drug gets infused, sometimes we can have a sensor, it can check the glucose level and release the anti-diabetic drug okay that is called infusors okay.

So it is kept inside the body and the drug gets released from time to time or based on certain conditions. Skin patches, you must have heard about nicotine patch so the drug which is in the patch slowly gets into the body okay. Pro-drugs, I explained it is a drug and another molecule connected through a bond, the other molecule helps the drug to maybe cross the membrane maybe improve the stability.

But inside the body the presence of enzymes may degrade and the drug gets released and then it is in active form okay. So the pro-drug is not active but once the drug gets released inside the body because of some enzyme action then the drug becomes active okay. Liposomes, drugs could be in capsulated in liposomes okay they are highly hydrophilic systems. Targeted drug delivery, we can target to a particular side using certain cues based on pH or temperature or presence of some other enzyme, antibody directed.

So as you know antibody, antigen type of combinations so the drug will go and bind to only one particular antigen and not to any other antigen. So lot of different approaches by which drug could be targeted okay and also the release profile could be extended over a long period of time okay. So we will continue again in the next class on this topic of ADME. Thank you very much for your time.