Computer Aided Drug Design
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Lecture – 05
Drug - Properties

Hello everyone, Welcome to the course on computer aided drugs design. In this class, we are going to look at drug properties. So it is not only that a drug should have very high activity whether killing bacteria, or whether killing cancerous cells, or whether reducing the glucose levels in the blood it should have large number of important properties. I did introduce some of those properties, but we will start going more in detail okay so because it has taken inside the human body okay.

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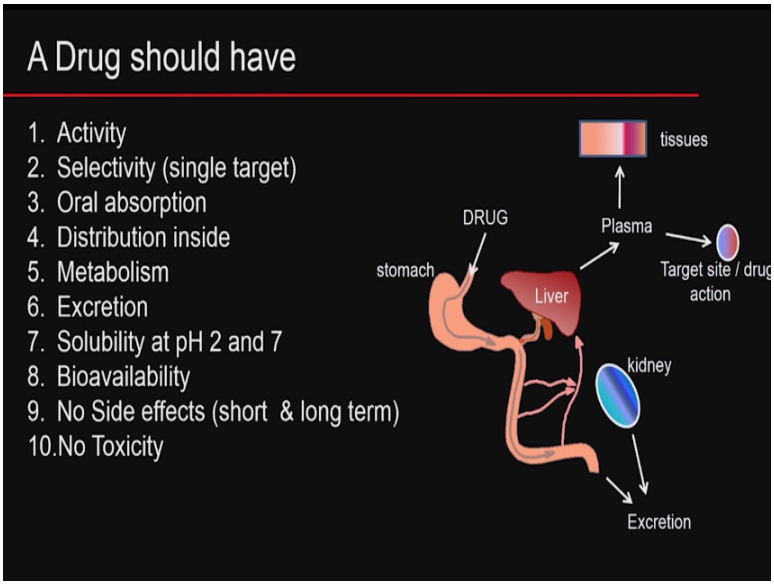

It is consumed by all of us mostly orally because large numbers of drugs are consumed orally when compared to intravenous or intraperitoneal. So the drugs should have activity of course, it should have good activity, and it should have selectivity for single target. We do not want the drug acting on several targets; thereby it may be causing side effects. So it should be very specific to one particular target.

So if it has to kill a particular type of tumor, it should go and attack only that. If it has to go and block an enzyme in certain pathway, it should go and block only that enzyme not all other

enzymes in that pathway. Then, it should have oral absorption because as I said most of time we take drugs orally because nobody likes injection and different modes of the intake of drugs and it should get distributed inside the body because as soon as it reaches the blood the drug has get distributed everywhere.

And then it will go and reach the target site and of course it gets metabolized inside okay in the body. So let us look at this particular figure which I have drawn, so generally we take a drugs orally so it reaches the stomach okay there is an absorption in the stomach and then as it goes down in the duodenum there is absorption inside into the blood stream and of course the liver is there which starts degrading because liver is a wonderful gatekeeper so there are many enzymes p450 types of enzymes okay.

They degrade, the drugs get metabolized so only small amount of drug is available in the blood stream when compared to what the drug we take here. So the drug does not get absorbed in the GI tract or the duodenum it gets excreted it is a waste okay and again inside if there is a metabolism and then it goes liver to kidney and then drug again gets excreted through urine again that is a waste.

So what is available in the plasma could be much less than what is taken in orally and of course it does not stop there. Some of the drug can even get absorbed in the tissues. So the amount of drug that reaches the target site where it has to go and act may be much, much less when compared to drug which we take here okay. So this is the effective concentration where it acts whereas this is what we take okay.

So this ratio is also called bioavailability, and so imagine I have a swelling in my finger and we all know we take drugs like ibuprofen, they are called nonsteroidal anti-inflammatory drug so it comes in whatever gets absorbed goes into the blood stream, but whatever does not get absorbed into the GI and duodenum is wasted. The liver starts degrading the ibuprofen and so it may come out through urine again it is excreted.

And there could be some absorption from the blood stream into the tissues so the concentration that reaches my finger they reduce the swelling in my finger may be much, much less when compared to what I take orally okay. Because this is the concentration which acts on the target side and the action will depend upon this concentration and not this concentration. So lot of things happened for the drug when it moves from your oral to the target site okay.

Things like absorption, distribution, metabolism, because it gets metabolized inside the body, enzymes like oxidoreductase, lipases, okay and so on actually, esterases and so on okay. Then of course it gets excreted which may not get absorbed in the stomach or the duodenum or it can get excreted from the kidney through urine. Then solubility as you know the pH of the stomach is 2 whereas the pH down the line can go up 2, 3, 4, and all that and the pH in the blood stream is 7.4.

So it has to be soluble at these pHs. So that is a big challenge for that drug. It should be soluble at 2 or it should be soluble at 7 otherwise it will start precipitating okay. Some of the natural products might not be soluble here and they may be soluble here and so on actually okay and so many of the drugs are made into salts so that it improves the solubility here and then this bioavailability that means the concentration of the drug at the target as against the concentration that is given orally okay that is called bioavailability.

If the bioavailability is large, so even with small concentration we achieve reasonably good concentration here and the bioavailability is poor even if you take very large concentration of the drug, the concentration available, the target site may be very, very low. For example, I have a fungal infection in my foot okay so the concentration at the foot should be higher so that it kills the fungus okay so I take an antibiotic.

What the antibiotic goes through all these processes? Some of them gets absorbed, some of them gets excreted, then some of them get metabolized in the liver and goes away as urine. Some of them might get absorbed in my tissues and so the concentration that is reaching my foot if it is less than the minimum inhibitory concentration required to kill the fungus whatever I have taken is of no use.

So the concentration of the drug at my foot should be higher so that the fungus gets killed. Otherwise, doctor has to prescribe much higher dose which can lead to toxicity in the stomach or liver, but it may not act to the target site because it is not reaching the minimum inhibitory concentration. So the bioavailability of a drug should be high. Generally, (()) (07:14) 30-35% at least we should have a bioavailability that means 67% of the drug is wasted somewhere okay.

Either as excreted, either as tissue deposits, either as metabolized too much metabolism taking place inside the body because some of the structure features are so bad that it gets either oxidized or it gets esterify and so on. Then no side effects that means drug should not have any side effects short or long term okay.

So we do not want either short term that means within a few months may be vomiting or increase in blood pressure or long term it should not give cardiovascular problems or some other side effects in the long term okay and then no toxicity of course it should not have any toxicity okay there are 10 points which you saw and it is not complete you are going to see some of them.

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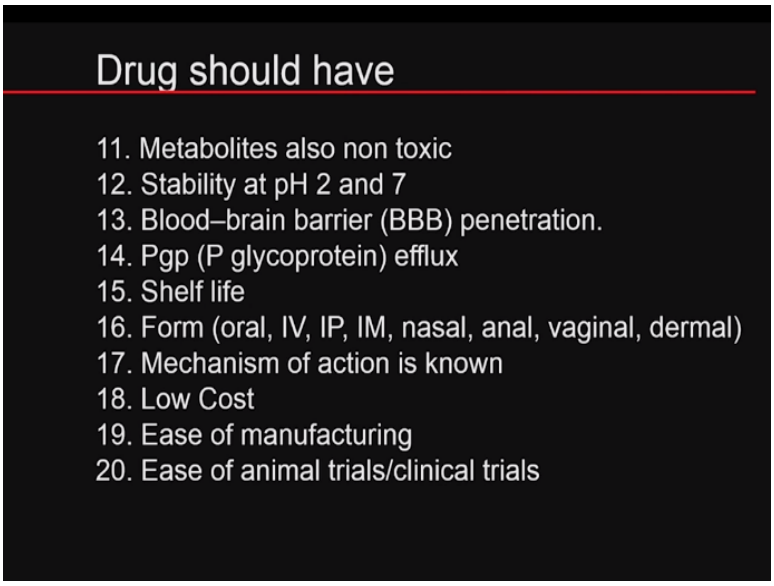

Metabolites also should not be toxic, because the drug might not be toxic, but it degrades into smaller molecules which may be toxic so we do not want. The drugs should be stable just like soluble at these 2 pH conditions. It should also be stable at these pH conditions okay suppose

there are ester bonds or amide bonds we start degrading or getting hydrolyzed at acidic pH okay. Then there is something called blood-brain barrier.

We will talk about this later quite a lot. These blood-brain barriers separate the entire body with the brain okay it prevents viruses, other toxin entering the brain. It allows only oxygen, nutrients to pass through okay so the drugs which we take for curing the human body should not enter the brain and start disturbing the brain function okay. So there is something called blood-brain barrier. We do not want the drug to penetrate the blood-brain barrier okay.

You do not want ibuprofen penetrating and causing some issues with the brain. Of course, there are drugs which are meant for neurodiseases okay, central neural system-related disease at that time we want the drugs to cross the blood-brain barrier whereas normal drugs which are used for our body functions should not be crossing the blood-brain barrier. We will look at that more in detail later okay.

And there is sort of P gylcoprotein type of proteins which acts as a effluxing pumps that means if they see any foreign molecule they capture it and throw it away okay so that way they keep the body free of toxins especially in the blood-brain barrier region especially the pregnant woman they all have quite a lot of this. So we do not want the drug to get effluxed out then it becomes a waste. So effluxing happens, the drug will get thrown out into the urine.

So we do not want that to happen because we lose drug whatever is present inside the plasma. Then Shelf life, of course you make the drug, the manufacturer makes it and then it is sent to pharmacy and then the patient buys it. So it may take 3 months, 6 months, so the drug should have enough Shelf life that is very important. It should not start degrading. It should not get oxidized and so on and you have to decide on the form is it going to be an oral drug.

If it is going to be intravenous, intraperitoneal, intramuscular, nasal, anal, vaginal, dermal so depending upon the type of drug intake, they may formulate it in different ways okay. So that is also very, very important okay it should be easily made into a powder form or it should be made

into a solution form and so on actually, and we should also know the mechanism of action. You should know how the drug acts?

Which enzymes it blocks or which proteins or which genes it down regulates or up regulates that is very, very important nowadays that question is being asked by the FDA that is the food and drug administration of USA before giving approval. They do not just give approval for any molecule which shows very good activity. It was so many years back but in the past 25-30 years without knowing the mechanism of action, drugs are not approved by FDA and of course cost.

Cost plays a very important role and if it is a new drug, new chemical entity introduced so pharma companies will charge very, very high prices to recover the RND cost such drugs are not sold in countries like India or third world countries, but once the drug comes out of the patent okay once the drug comes out of the patent then it becomes a genetic drug then the cost comes down okay.

Some of the drugs for example for tuberculosis, HIV, malaria generally it is expected the cost of the drug has to be low because it has to reach out to very poor population whereas some of the cancer drugs which are being introduced very newly may cost thousands and thousands of rupees okay whereas a malarial drug will cost only few rupees. Then ease of manufacture of course bioprocess how do you manufacture this is it easy to manufacture.

That is also very important you should be able to manufacture it in very simple steps so and then the ease of animal trials because once the new chemical entities establish in the lab or the trials have to be done on animals then and human volunteers so it should be easy to perform these trials and monitor the entire operation. So you see almost 20 requirements are there so it is not just activity, but a large number of requirements are needed so that you can be very sure that it can pass out as a drug.

So many, many active molecules in your lab do not cross the approval because they have one of these problems okay so they may be having one of these problems here or they be having one of the problems listed out in this. So the drug gets thrown out. So the chemistry plays a very

important role when you design drugs. The chemical structure plays a very important role in designing on the property. So the structure-property relationship is very, very important.

Which structural features improve its stability? Which structural features reduces metabolism? Which structure features improve bioavailability? Which sub-structural features improve solubility in the GI, okay. So, all these are very important to know so you should have good knowledge about medicinal chemistry, biochemistry, physical chemistry, and so on actually. Okay. So what are these structural features?

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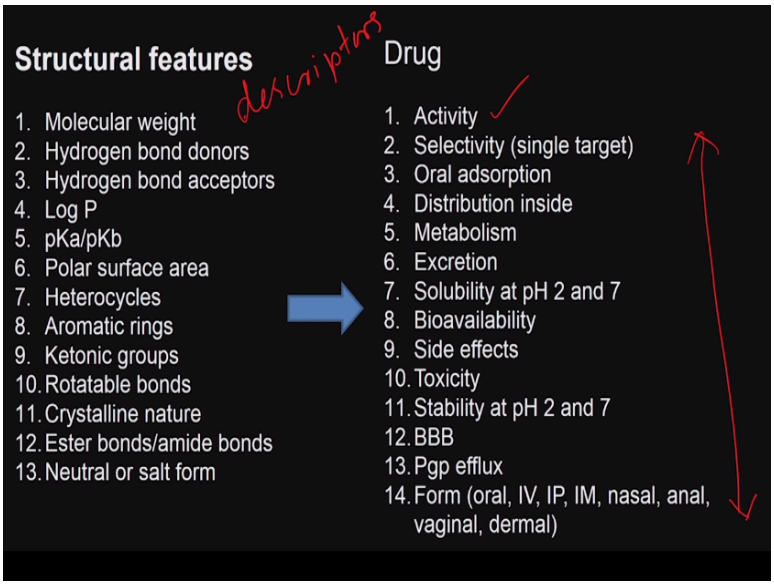

Molecular weight, hydrogen bond donors, hydrogen bond acceptors. Hydrogen bond donors means groups like OH or NH, hydrogen bond acceptors mean oxygen, nitrogen like that. Log P is a very, very important property. Log P tells you the hydrophobic, hydrophilic balance of the drug that means it should neither be hydrophobic or it should neither be hydrophilic and if it is too much hydrophilic it will dissolve nicely in the stomach.

But it has to cross the GI which is made up of lipids, which is hydrophobic so it will not cross. If it is too much hydrophobic the drug will not dissolve in your stomach fluids, but it will be able to easily diffuse through the GI because GI is very hydrophobic okay that is called Log P. So Log P is a ratio of the hydrophobic to hydrophilic balance. Then comes pKa/pKb, that means

dissociation and mild acids and mild base conditions what is the polar surface area okay polar groups are like oxygen and nitrogen.

How many heterocycles are there that means cyclic groups which contains nitrogen, oxygen, how many aromatic rings are there? How many ketonic groups are there? How many rotatable bonds? Once you have rotatable bond drug is very flexible so it can easily fit into an active site, a crystalline nature whether it is crystalline or not. too much crystallinity the drug will not be soluble if it is amorphous it is soluble how many ester bonds are there, amide bonds are there because ester bonds can easily degrade with esteraces, amidases.

If these enzymes are present in the body, they could get metabolized. Neutral or salt form? Is it a neutral or salt form? So all these features and these are the activity, selectivity, oral absorption, distribution inside the body, metabolism, excretion, solubility at pH2 and 7, bioavailability, side effects, toxicity, stability, blood-brain barrier, Pgp efflux, forms all these are decided by the structure features okay. We also call it structure descriptors. We call it structural descriptors or structural features and so on.

So we call it features, descriptors, okay sorry descriptors, features, structural descriptors okay so these structural features or descriptors determine various properties of the drug so as a medicinal chemist you should be able to play with these to arrive at these and of course activity is the most important, but you cannot forget activities the most important, but you cannot forget all these. These are all very, very important for drug to cross the FDA approval okay and so these structural features, structural descriptors, determine all these parameters okay.

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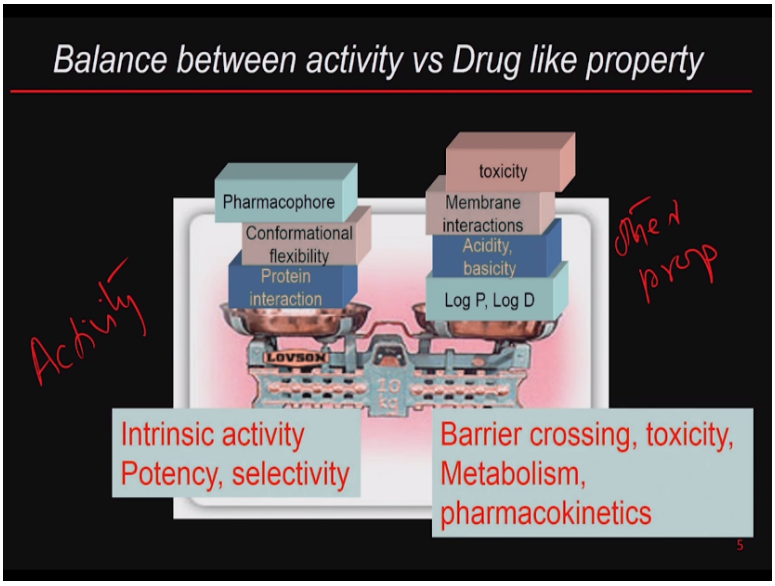

So what happens? Sometimes we need to take a balance between activity or potency or selectivity as against these other drug likeness properties whenever it crosses these GI tract, toxicity, metabolism, pharmacokinetics, okay. What happens so you need to balance between activity versus other properties. So sometimes you will have a very active drug, but it will have very poor properties may be it does not cross the GI tract or may be it gets degraded.

Whereas the second most active drug in your lab may have all the other properties. So it is better to take the second most drug into the market through the clinical trials rather than but on the first trial or make modifications to the structural features of the drug okay it makes a modification to the structure features okay so that we get better if there are any issues on one of those properties okay.

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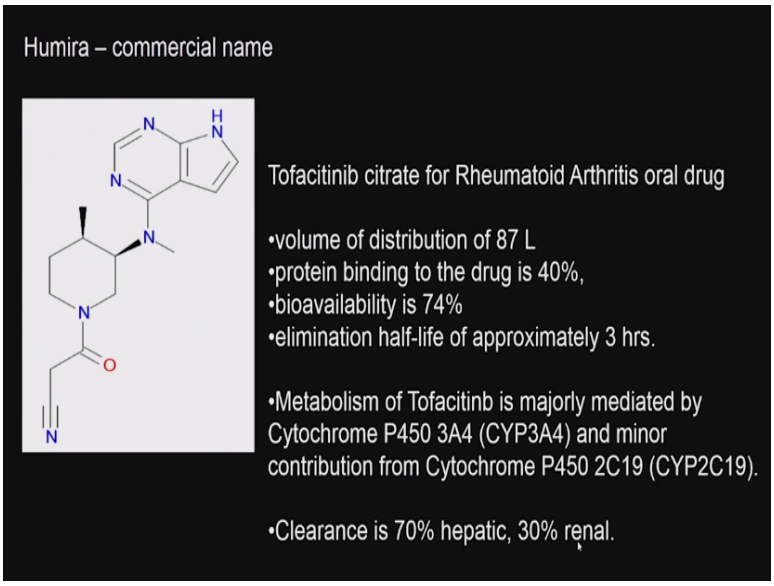

Let us now look at some of the drugs which I mentioned commercial drugs in the market which I had mentioned as few top selling drugs and we will look at some of those structural features. Okay. This drug is called Humira, Okay, this is for rheumatoid arthritis is taken as a oral drug, okay, so the volume of distribution is 87 liters, that means it gets distributed in the blood as well as in some tissues, and when you have the very large volume of distribution inside the body the concentration of the drug goes down.

So that means effective concentration is much less. Okay. It binds to a protein, yeah, if the drug binds to a protein by about is about 40%. Okay and so its bioavailability is about 74%, that means if I take 100 milligrams of the drug orally 74 milligram of the drug is available at the target side which is good. Generally, things like 70, 75, 65 are reasonably good. Okay. It gets eliminated from the body. The half-life of the elimination is 3 hours. Okay.

That means 50% of the drugs get eliminated from the plasma in 3 hours. It is also good. We do not want too much of drugs staying into the body for a very long time and of course the elimination is very fast. The drug action goes down very fast. So you may to keep by taking the drug quite often, if the elimination is very, very slow then there is an accumulation of the drug there could be other problems as you go long. Okay.

The metabolism drugs is a metabolized by this particular enzyme called cytochrome p450, okay, so large number of enzymes metabolize that. Okay. This is the one of the top selling drugs in the market. So the clearance is 70%. So it gets cleared through the hepatitic clearance okay through the liver and this is through the renal clearance okay.

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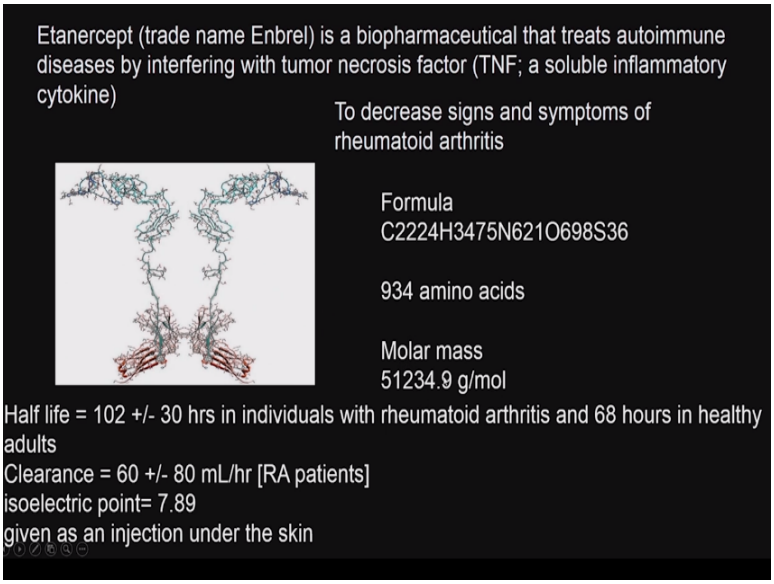

Let us look at another one it is called Etanercept okay. This is a biological product as you can see it is like a it is protein okay, it treats autoimmune diseases by interfering with TNF a soluble inflammatory cytokine to decrease the signs of rheumatoid arthritis okay. So it treats autoimmune disease and it is large molecules, it is biomolecule. Okay. As you can see 51,234 Dalton, it has got 934 amino acids in it. So obviously, it has given as an injection under the skin.

So as you can see if the molecule is smaller in molecular weight like in the previous case it can be given oral, but as this is a large molecule obviously proteins cannot be taken in orally because when the pH of 2 in the GI to stomach it may get degraded and it will also not cross the GI tract. So it is half-life is quite large, 102 hours okay. It is clearance is 60 to 80 milliliter per hour. It is isoelectric point that is 7.89 that pH at 7.89 it has got 0 charge okay. So it has given as injection. So because it is a protein large molecular weight.

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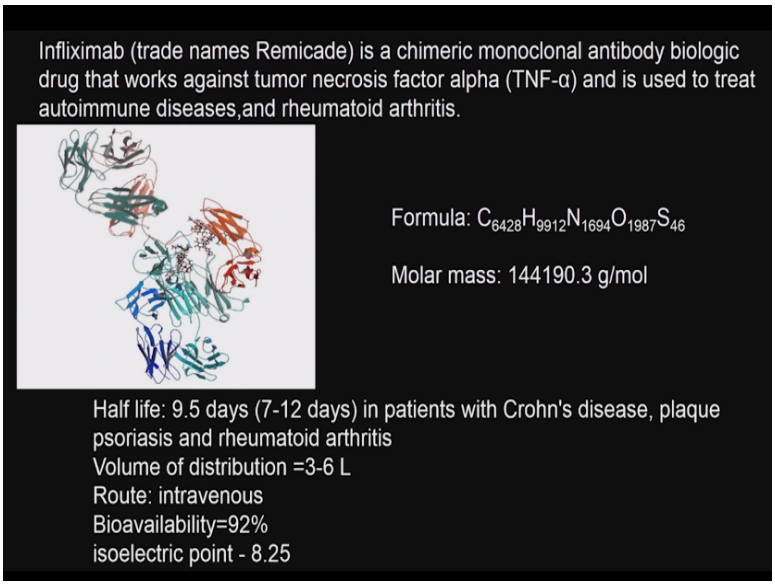

Let us look at another one this is chimeric monoclonal antibody that works against TNF alpha. It is used to treat autoimmune diseases and rheumatoid arthritis again this is a large molecule. It is protein. It is a chimeric protein okay. So 144190. Okay. So obviously it has given intravenous here as you can see it is given intravenous. Bioavailability is excellent 92% because it is given intravenous.

There is no problem about crossing the GI, pH stability all those things, volume of distribution is 3 to 6 liters. So very low volume, so obviously the concentration in the blood plasma region is very high.

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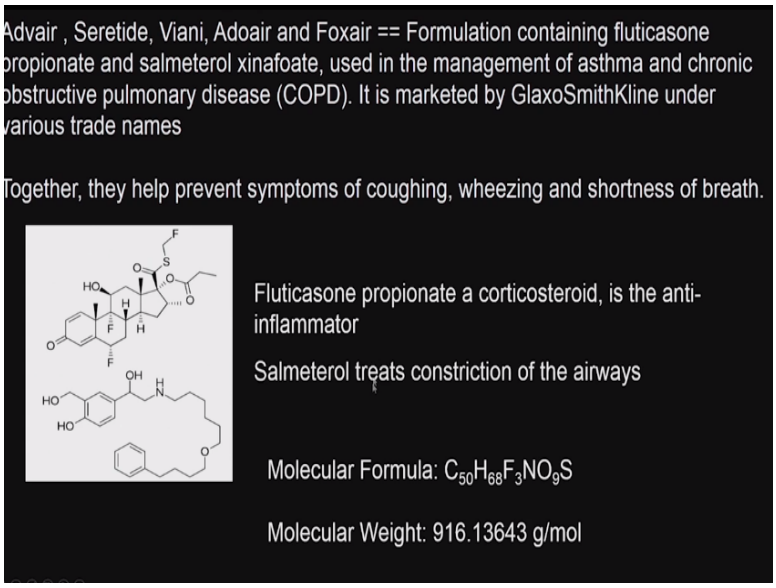

Now look at another drug. This is a small molecule drug. This is the mixture of the 3 drugs, Advair, Seretide, Viani okay. It is a formulation containing so many different used in the management of asthma and chronic constructive pulmonary disease. Okay. So it contains some anti-inflammatory. So it contains drug which will dilate the pulmonary. They help prevent symptoms of the coughing, wheezing, shortness of breath so on okay and so obviously the molecular weight 916 grams mole. Okay.

So it is basically constriction of airways for anti-inflammatory.

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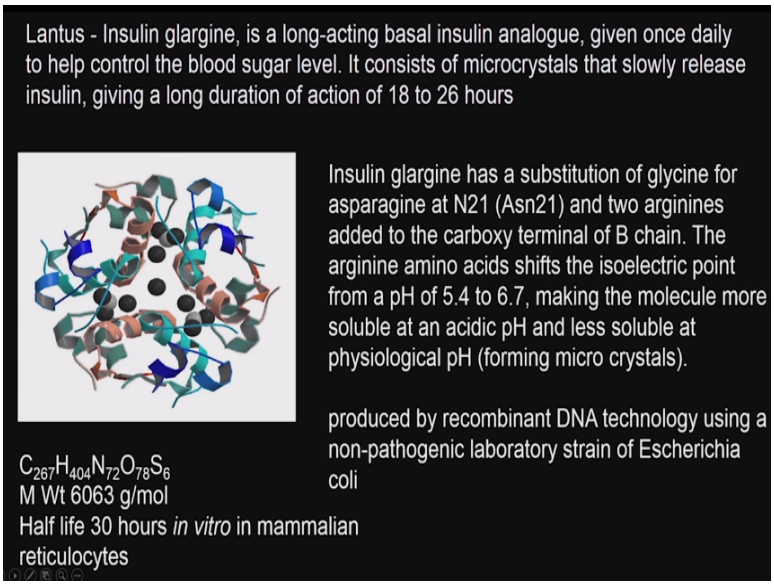

Look at the another one, these are long acting basal insulin analogue okay so insulin analogue means it is supposed to control the blood sugar level. Okay. It is a long duration long action so it is 18 to 26 hours. Okay. It produced by recombinant DNA technology. It is an isoelectric point of 5.4 to 6.7, half-life 30 hours in mammals, 6063 okay. So it is not given orally, it has to be given through intravenous. Okay.

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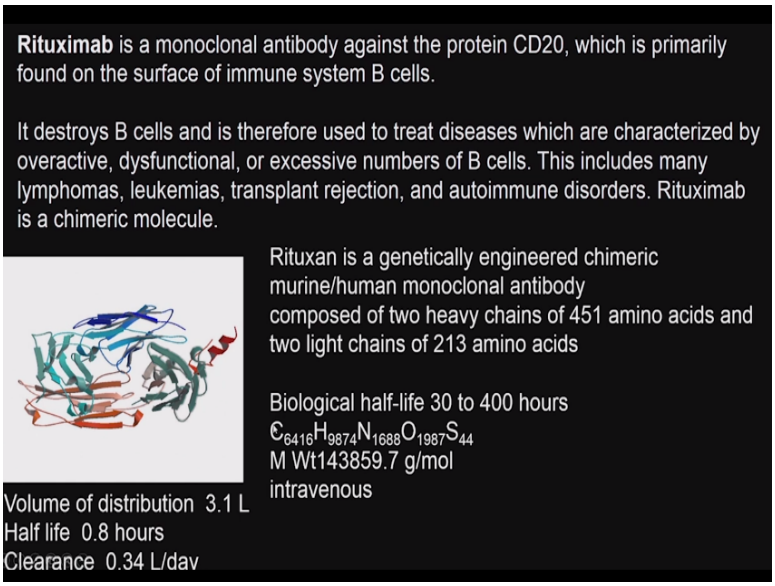

Look at another drug. A monoclonal antibody against the protein CD20. So one important thing you notice that all the commercial drugs, top selling drugs, which I am showing here the mechanism of action of these are well known. Okay. It is again, it is 143859 large molecules so obviously it is given intravenous half-life is 30 to 400 hours. Okay. Because it is a protein like it has got 213 amino acids 2 heavy chains 415 amino acids and 2 light chains, 2 heavy chain 2 light chain 213 amino acids. Okay.

This is given meant for autoimmune disease okay leukemias and so on actually. The volume of distribution 3 liters, half-life is 0.8, clearance is very slow 0.34 per day, so it can act much longer.

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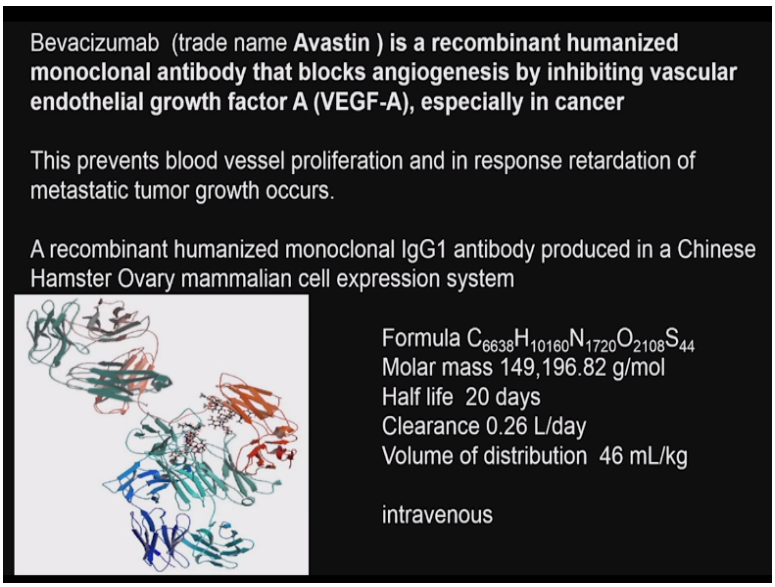

Look at another drug. This is called Avastin. It is a recombinant monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor, A(VEGF-A) it is called. So it involves it prevents cancer, it prevents blood vessel proliferation okay and tumor growth okay. Of course it is a recombinant growth product and it has given as intravenous. Because look at the molar mass 149196, half-life is quite good 20 days.

That means it last inside the body for a very long time. That is why clearance is also very low 0.26 and the volume of the distribution is 46 ml very, very low so little concentration I mean little days inside you can have large concentration.

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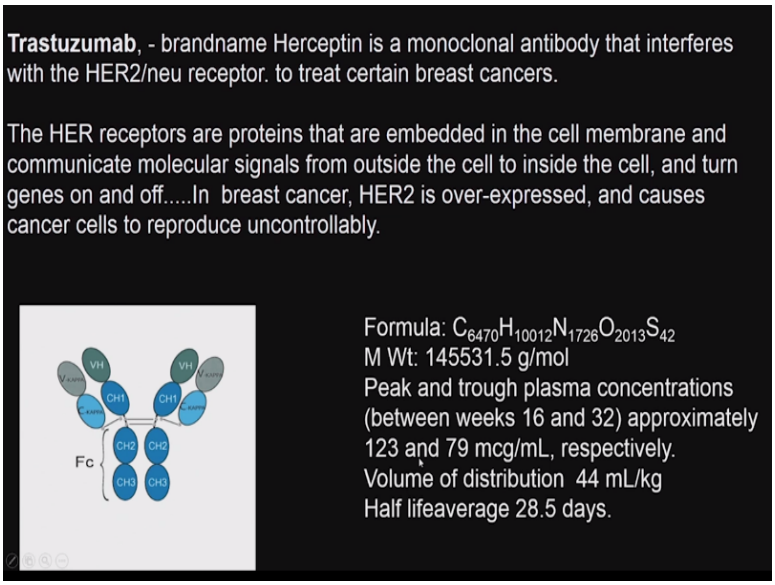

Look at another drug. Trastuzumab. That is the brand name Herceptin. It is a monoclonal antibody that interferes with HER2 neu receptor to treat certain breast cancers. Okay. It is a huge molecule 145531, half-life of 28 days, the volume of distribution is 44 ml per kg that means the volume is very, very low. So you can achieve very large concentration with this drug okay and so this is also given intravenous.

So as you can see many of these biological molecules have very large molecular weight and so most of them are given for intravenous because of it is stability at GI pH of 2 as well as it will not be able the cross the barrier.

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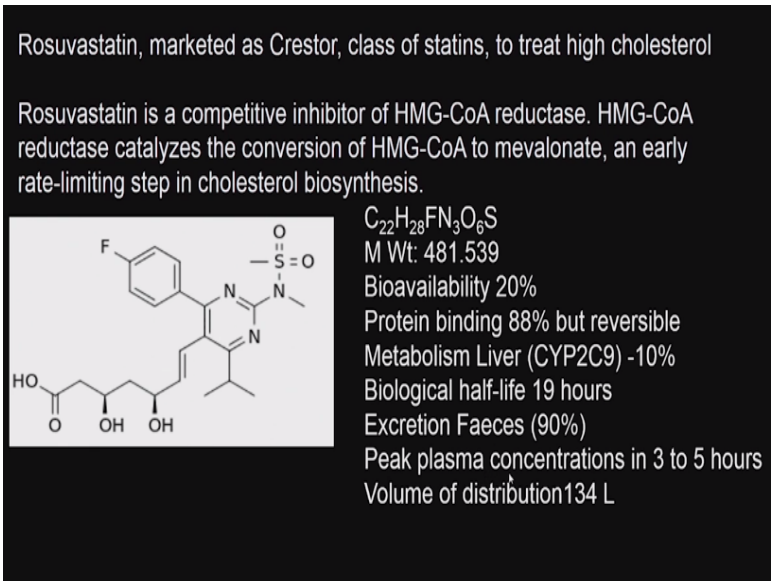

Look at this drug. Rosuvastatin, okay. This is a class of statin should treat high cholesterol. Okay. It is a competitive inhibitor of HMG-CoA reductase. Okay. And small molecular weight 481 and look at this it has got very low bioavailability because it is taken orally that is why the bioavailability is very low 20%. So if drugs are taken intravenous you will have very high bioavailability, but nobody likes injection, everybody likes oral drug.

Once you have oral bioavailability could be one of the problems. Why is it so, it binds to lot of proteins inside the body. Okay. It is reversible but because of this binding concentration of the drug in the plasma comes down. Okay. Peak plasma concentration at 3 to 5 hours, volume of distribution is very large. You can see 134 liters and many of the protein type of drugs have very low volume of distribution, whereas these types of small molecules are very high volume, so the concentration available inside could be very low.

Okay. So statins are big business for reducing cholesterol. There are huge number of statins. Atorvastatin, cerivastatin, pitavastatin, rosuvastatin and so on, but this particular molecule contains sulphur, other molecules do not contain sulphur. So statins are meant for high cholesterol and it is a big business and annual sales could run into billions of dollars.

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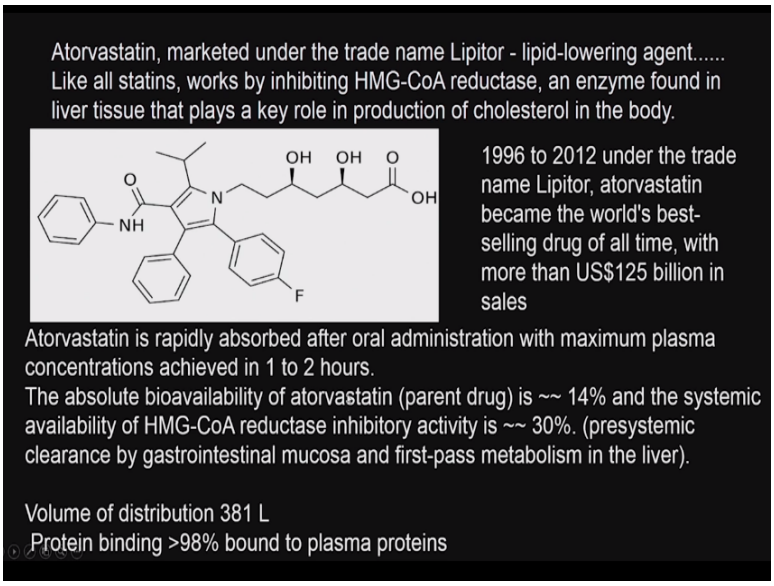

Look at the other one. That is the Atorvastatin, marketed under the trade name of Lipitor. Once upon time it was making 10s of billions of dollars okay for reducing the cholesterol by acting on this HMG-CoA reductase okay. As you can see 1996 to 2012, Lipitor made 125 billion sales okay that is a huge deal business okay. Again the volume of the distribution is 381 liters, so obviously the concentration inside will be low.

Because lot of protein binding takes place and the bioavailability is also very low 14% and systemic availability is 30%. So it is quiet low. Okay, maximum concentration is achieved in 2 to 3 hours so it starts acting very fast. Okay.

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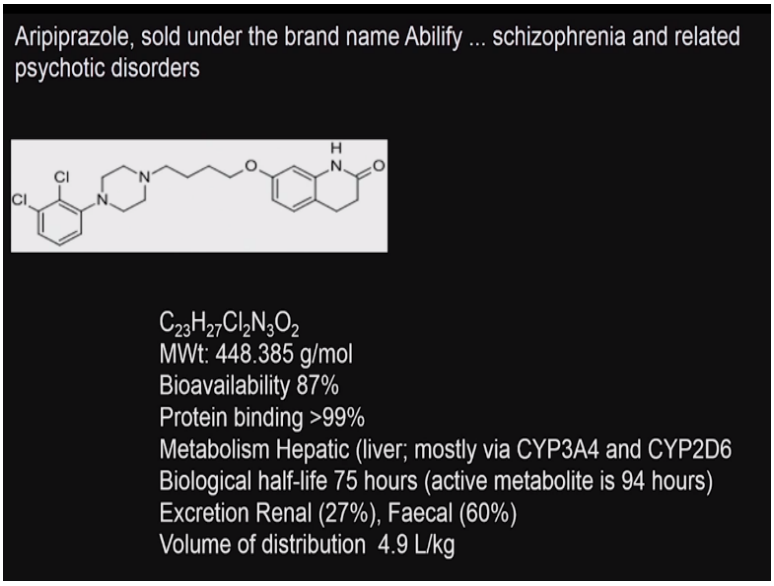

Look at the another drug. This is also a small molecule under the brand name Abilify okay. This is meant for psychotic disorders. It is called CNS types of disorders, central nervous system related disease, so it has to cross the blood-brain barrier. This is small molecule 448 molecular weight, bioavailability is quite good 87% and binds quite lot to the protein, it gets metabolized by cytochrome enzymes in the liver okay. Biological half-life is 75 hours.

It is excreted renal by 27 fecal by 60%, volume of distribution is reasonable. So large number of highly successful commercially successful drugs structures and properties which we saw now some of them are biomolecules proteins and obviously they are given us intravenous small molecules are given orally when they are given orally bioavailability goes down and as you can see.

When they are given intravenous bioavailability is very, very large proteins have very low volume of distribution, so peak concentrations can be very high whereas small molecules have very large volume of distribution so peak concentrations could be very low. So we look at very important properties which a drug should have before it becomes successful. So you need lot of knowledge about biochemistry and medicinal chemistry, physical chemistry.

So that you can combine all these aspects with the biological activities so that one can come up with a very successful molecule. So we will continue more about this drug property as we go along. Okay. Thank you very much for your time.