Computer Aided Drug Design
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Lecture - 08
Drug Solubility/Permeability

Hello everyone, welcome to the course on computer-aided drug design. We will continue on the topic of solubility then I will start introducing permeability. Solubility and permeability are sort of contradicting each other or conflicting. Solubility, we are talking about solubility in the GI that means it has to have good water solubility that means it should be a polar but when you talk about permeability it has to cross the membrane, the lipid bilayer and reach the blood stream.

That means it has to be hydrophobic or lipophilic, so it should have less of hydrophilicity. So this solubility and permeability are always at loggerheads. So we need to balance the property of the drug so that both are satisfied at the same time that means it should have enough water solubility and then it should be able to permeabilize through the GI membrane and reach the blood stream.

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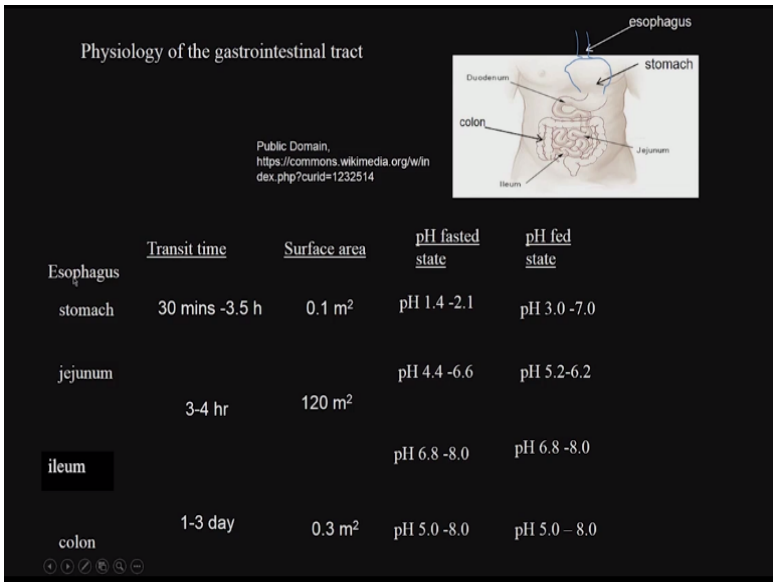

Now many factors affect this solubility. Yesterday, we did introduce this. If you look at the transit time in various parts of the GI, you know starting from esophagus stomach 30 minutes to 3.5 hours whereas if you go to jejunum it could be 3 to 4 hours and then the surface area if

you look at we call this small intestine 120 meter square whereas stomach the surface area is very small 0.1-meter square.

The pH in the stomach is very, very acidic 1.4 to 2.1, as we go down into the small intestine we go to almost neutral and basic and so most of the drug absorption should be taking place here because the surface area is very, very high. Colon, it is one to 3 days, surface area again is very low, pH is almost in the basic region, so we are moving from highly acidic to basic and then a low surface area, very, very high surface area, again low surface area and as you can see the transit time also changes.

So one is to consider all these if you are talking about drug absorption and drug solubility.

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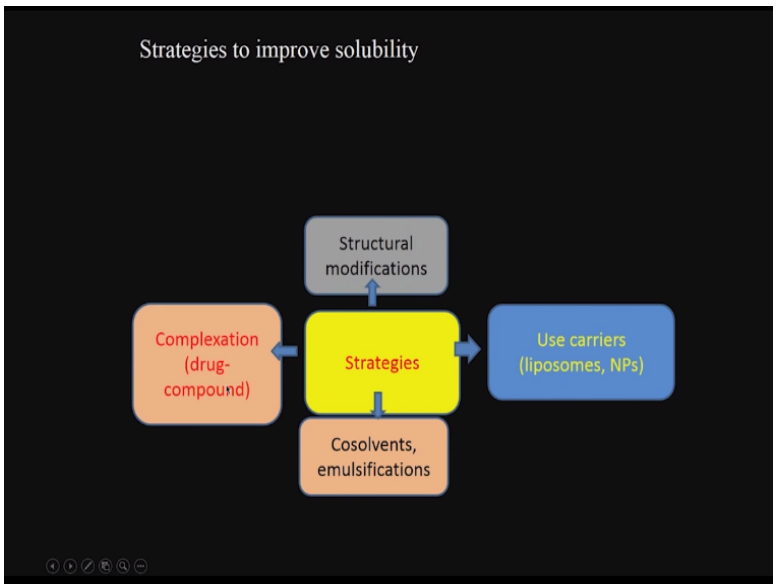

So we looked at what are the various strategies to improve solubility. We can do lot of structural modifications okay. Modify the Log P, make it more hydrophilic, make it into a salt, add polar groups okay, reduce the crystallinity of the material and so on or we can use carriers and nowadays there is lot of interest in drug carriers like nanoparticles, liposomes and so on okay.

Then, we can use co-solvents, we can emulsify the material. So that emulsion is able to dissolve nicely or we can add complexing agent okay so that it complexes with the drug and hence improve the solubility. These are strategies but generally these 3 items do not come under drug discovery. They will come later more of the pharmaceutics whereas these structural modifications which we are talking about we can call it drug discovery process.

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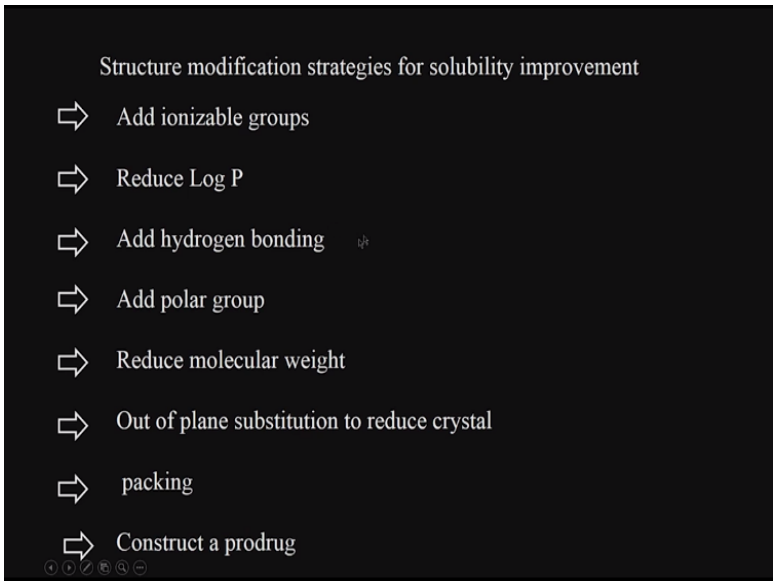

So adding ionizable groups, reducing Log P, adding hydrogen bond, adding polar groups okay, reduce molecular weight, out of plane substitution I showed you one so that crystalline packing is reduced, construct a prodrug, all these are various strategies which can improve solubility.

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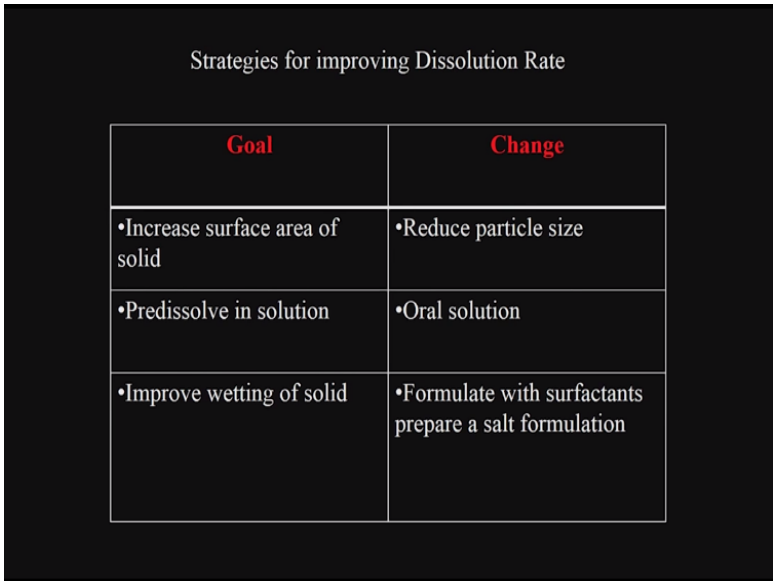

Now when you look at dissolution rate, how do I improve the dissolution? So not only it has to be soluble thermodynamically but it has to also be quite fast because as you can see in stomach it is only 3, 4 hours so if you want a fast acting drug it has to dissolve very fast. So dissolution is more of a kinetic so increase surface area. So by increasing surface area of the solid, it will start dissolving fast or reduce particle size.

Predissolve in a solution that means I can give an oral solution so that it is already dissolved in a solution form. Improve wetting of solids that means we can formulate with some surfactants, salt formulation, all those things we can do that will help the wetting of the solid. So these are some strategies for improving dissolution rate like I said dissolution is a kinetic whereas solubility could be more thermodynamic okay.

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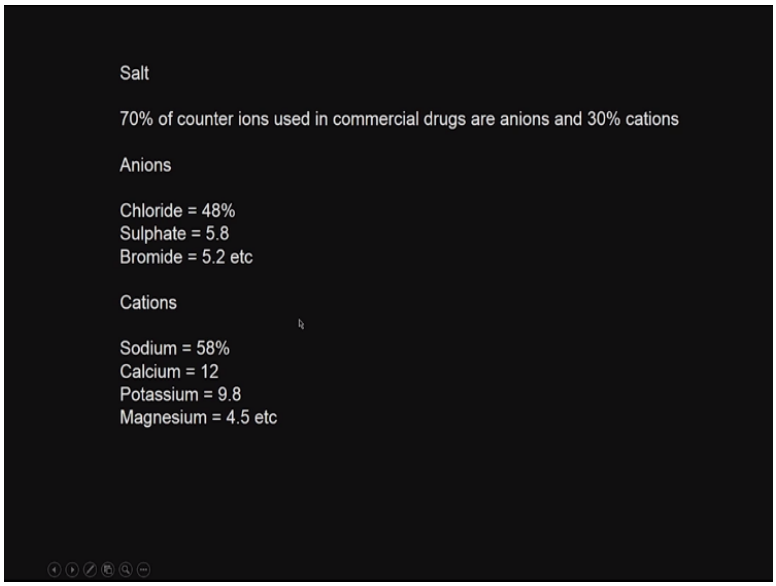

In generally drugs are manufactured as a salt form, 70% of drugs I would say are in salt form and out of that 70% of counter ions used in commercial drugs are anions and 30% of cations. So anions you could have chloride, sulphate, bromide in this order you know, predominantly drugs you will find lot of chlorides. If you look at cations, sodium salt or calcium salt or potassium salt and magnesium salt.

So these factors improve the solubility of the drug tremendously.

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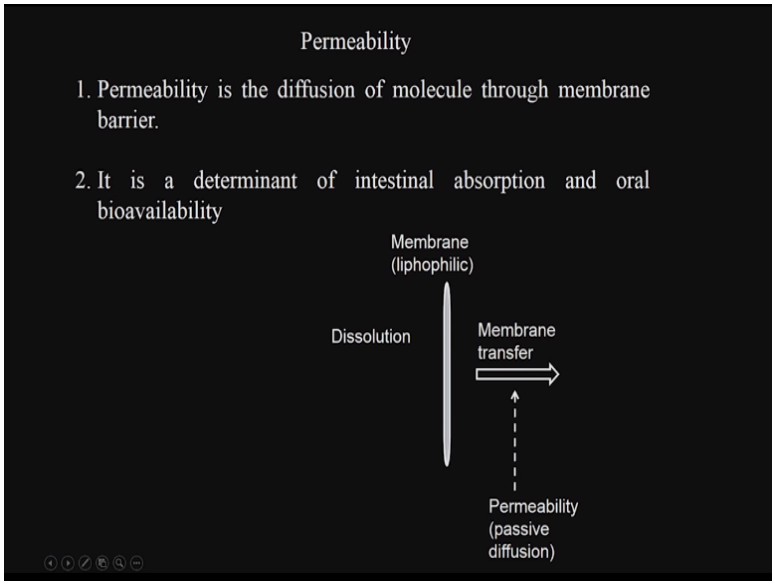

Now let us look at permeability. Permeability that is the diffusion of these molecule through the membrane, the GI lipid membrane which is highly lipophilic. Mostly, it is through passive diffusion okay, very little of active diffusion that happens mostly it is passive diffusion and so that means we have to have the compound reasonably lipophilic so that it passively diffuses.

So it is a determinant of intestinal absorption and oral bioavailability because your intestinal absorption and oral bioavailability depends on this permeability. If the permeability is very poor like I mentioned the drug could be solubilized but if it is not getting through the membrane so it may get excreted okay so that is the problem. So bioavailability can be poor.

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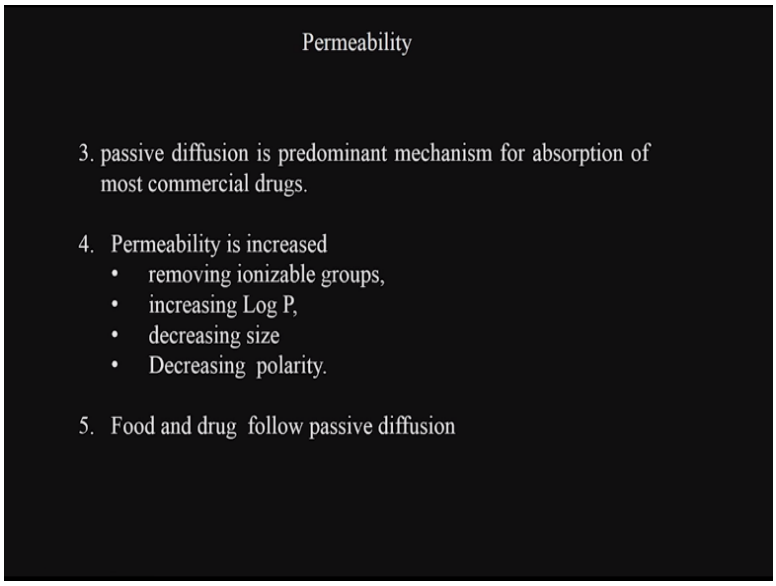

So many factors affect permeability. Generally, like I said passive diffusion is the predominant mechanism, commercial drugs even food generally it is passive diffusion. So

there is always a competition between food and drug and they both start behaving in a singular manner during these permeabilization hence that is why doctor sometimes say take the drug before food, take the drug after food because they start competing for the same diffusion through the GI.

So some drugs make it absorbed by the food and/or they may get prevented from passing through the GI membrane okay. Permeability is increased if I remove ionizable groups. If I have ionizable groups, then it becomes a polar compound and like I mentioned lipophilicity should be the factor which determines permeabilization through the GI so removing ionizable groups.

Increasing Log P, making it more hydrophobic, decreasing size, when you have smaller compound it diffuses better than larger, decreasing polarity that means remove the O-H groups and N-H groups and so on. We will look at some examples as we go down. Food and drug follow passive diffusion like I mentioned so there is always going to be a competition when you take food and drug together okay.

That is why it is always recommended for different types of drugs when to take before or after and so on actually.

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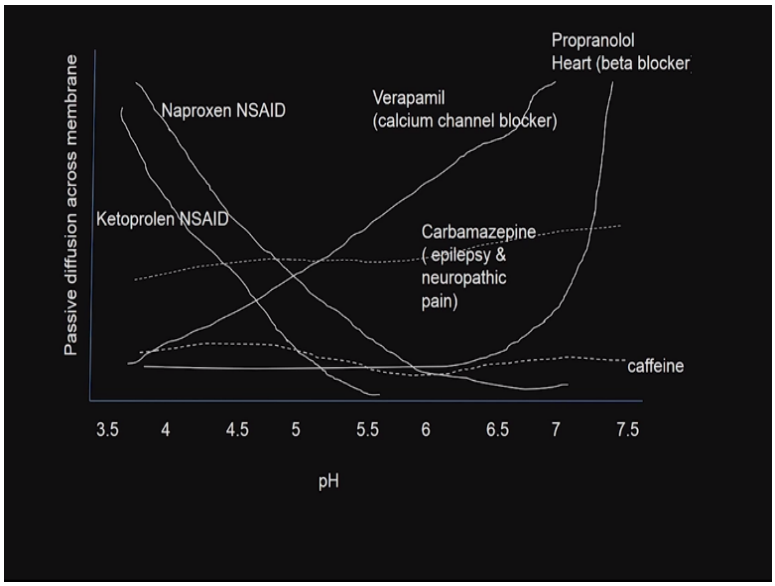

So this is a very interesting slide. Passive diffusion across the membrane as against pH okay. So we are talking this very low pH could be the stomach and it goes small intestine, large intestine and so on okay up to colon and so we see that the passive diffusion decreases for say

NSAID non-steroidal anti-inflammatory drug like Ketoprolen, another drug Naproxen, again it goes down.

So that means passive diffusion is very good in the stomach region okay and it becomes very poor as it goes to small and large intestine whereas if we take a calcium channel blocker Verapamil, it goes up with pH that means diffusion is much better down the line the small and large intestine rather than in your stomach and same thing happens here, a beta blocker like Propranolol where the diffusion is much better sharply rising at higher pH 6, 7 and all that actually okay.

If you look at caffeine diffusion is very, very low whether it is acidic or whether it is basic and same thing with epilepsy and neuropathic pain Carbamazepine, it is higher number but it does not change much with the pH condition. So you need to understand this. What is the favorable pH for it to diffuse as you can see some diffuses very fast okay in acidic condition and some diffuses very fast in basic condition okay?

So that plays a very important role in the entire drug action as well as its viability okay.

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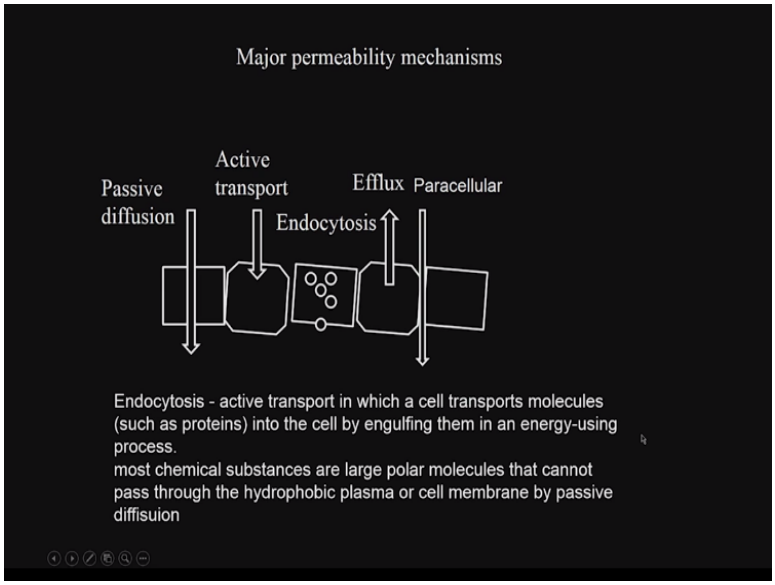

So we have predominantly passive diffusion taking place, then there could be specific transporters which may be collecting your compound and taking it across and there is something called endocytosis that is a mechanism, it is like gobbling up the food or drug or any compound that is endocytosis. Simultaneously, there is also efflux that means whatever is inside is thrown out.

This is a very important mechanism for the survival of the system. So efflux transporters are there, which throw out compounds which look foreign, its idea is to reduce the toxicity inside but it may throw even your drug out. This is the efflux transporters, so all these are taking place in membrane system and these are the major mechanisms by which these things happen.

So endocytosis like I said is the active transport in which cell transport molecules into the cell by engulfing almost like gobbling up in energy-using process okay so it does take up whereas your passive diffusion does not give any energy. So large chemical substances, polar molecules cannot pass through the hydrophobic plasma by passive diffusion. So they have to go through either an active process or endocytosis which is energy-using process okay whereas your passive diffusion does not use any energy.

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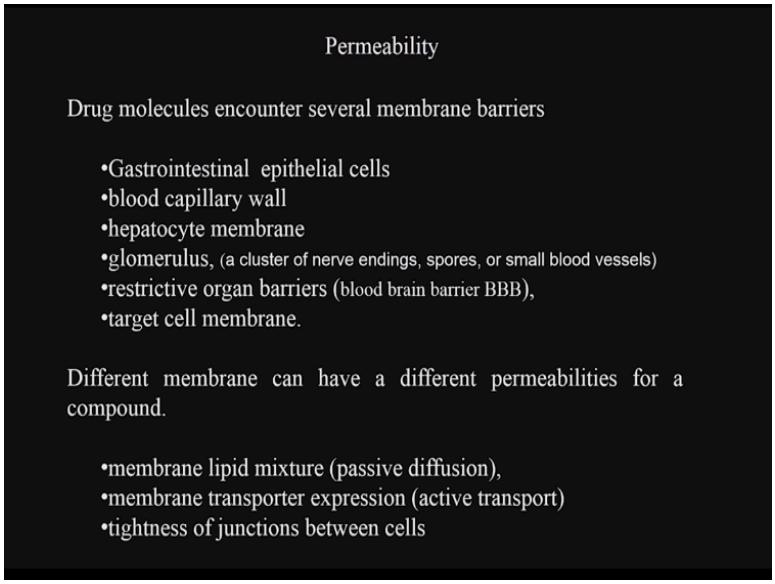

So permeability several membrane barriers. We have the gastrointestinal epithelial cells, blood capillary wall, hepatocyte membrane, glomerulus that is cluster of nerve endings, spores or small blood vessels, restrictive organ barriers that is the blood brain barrier we will talk more about this. There is a barrier which separates the brain from rest of the blood region okay to prevent toxins or viruses crossing and going into the brain.

It allows only small molecules glucose and oxygen and then target cell membrane so the drug has to encounter so many membrane barriers before it reaches its target site okay. Different membranes can have different permeabilities okay. Membrane lipid mixture passive

diffusion, membrane transporter active, tightness of junctions between walls, sometimes the junction walls are very tight so they do not allow any diffusion to take place unless it becomes very loose diffusion might not happen.

So different membranes may have different permeabilities okay, so permeability effects what can happen? They can affect the bioavailability because what is available at the target site of the drug maybe very, very small because it is not getting transported or permeabilized okay.

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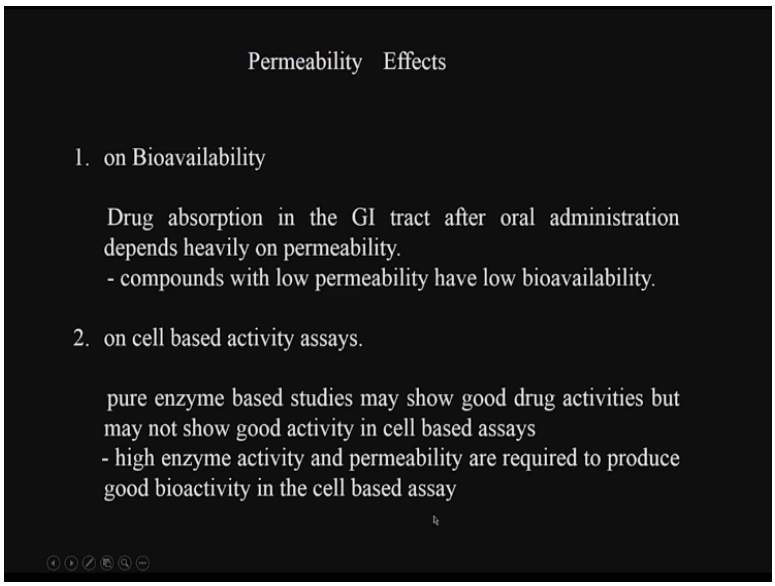

So after oral administration depends heavily on permeability of course okay and then compounds with low permeability have low bioavailability that is true. On cell based activity assay, so if I am doing any cell based assays so if the permeability pure enzyme based studies may show good drug activities but when I am using cell based system that is almost like a in vivo and it may show poor activity because the diffusion of the drug into the cell membrane maybe very poor.

So pure enzyme based studies may show very good positive results whereas when you do a cell based in vivo study it may show very poor result because of poor permeability. High enzyme activity and permeability are required to produce good bioactivity in the cell based assay, so cell based assay permeability plays a very important role.

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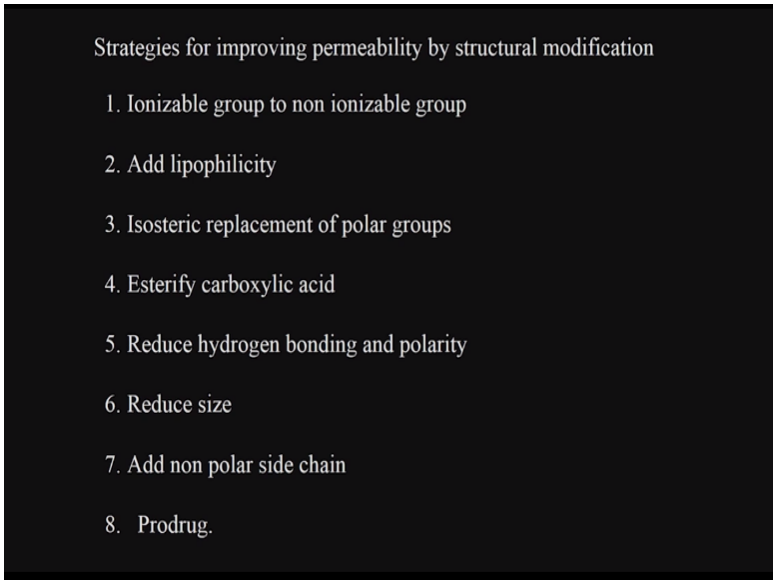

So what are the strategies, convert ionizable groups into non-ionizable. Like I said ionizable groups lead to polarity so make it more non polar. Add lipophilic group that means you are increasing Log P. Isosteric replacement of polar groups so if you have O-H group, make it O-CH3, N-H group make it N-CH3. Esterify carboxylic acid, so if you have acids it can become polar so we make it COOCH3 like.

Reduce hydrogen bonding and polarity, so if we have any hydrogen bonding groups O-H, N-H reduce them. Reduce the size so the material can transport easily inside. Add non polar side chain or do prodrug that means it is a complex like, it is not a drug that means it does not have any activity, when it goes inside the body it gets cleaved and the drug gets released which may start acting as a real drug that is called prodrug. So all these affects, let us look at some examples.

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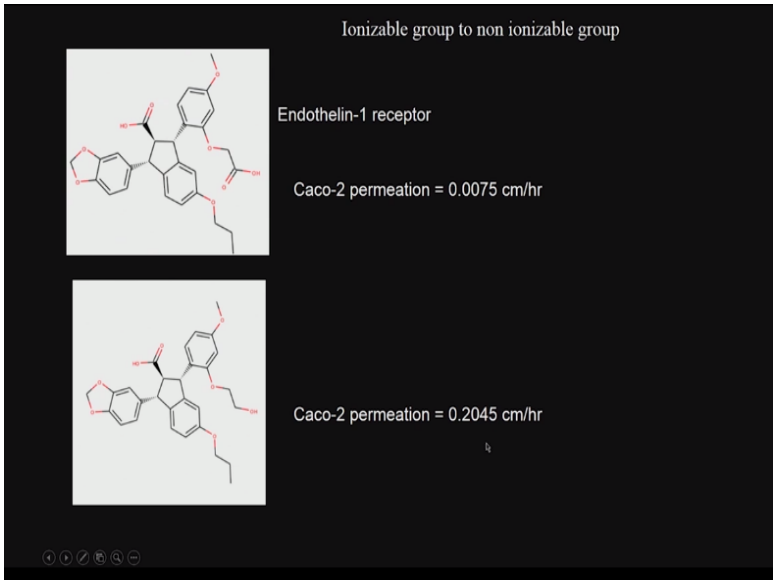

So we have an ionizable group as you can see there is an ionizable group okay and we are trying to convert that ionizable group. This is an Endothelin-1 receptor, the permeability through this Caco-2 is the cells which from the stomach, epithelium is very poor permeability whereas when I reduce the ionizable group to non-ionizable group because you have the acid here so we can have O- and H+.

We convert that into OH okay, it does not get ionized, look at the permeability, huge increase okay, 500 times increase maybe.

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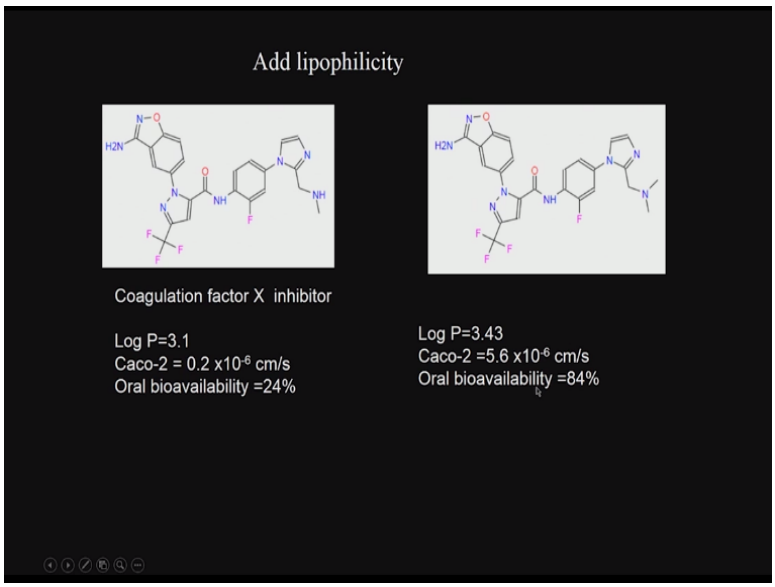

Add lipophilicity that means make it highly more Log P, so this is a coagulation factor X inhibitor okay and you are adding a lipophilic group into this okay. So that Log P increases from 3.1 to 3.43 and oral bioavailability also increases, there is an extra CH3 added so Log P

increases little bit only but look at this the permeability has increased and the oral bioavailability has increased tremendously.

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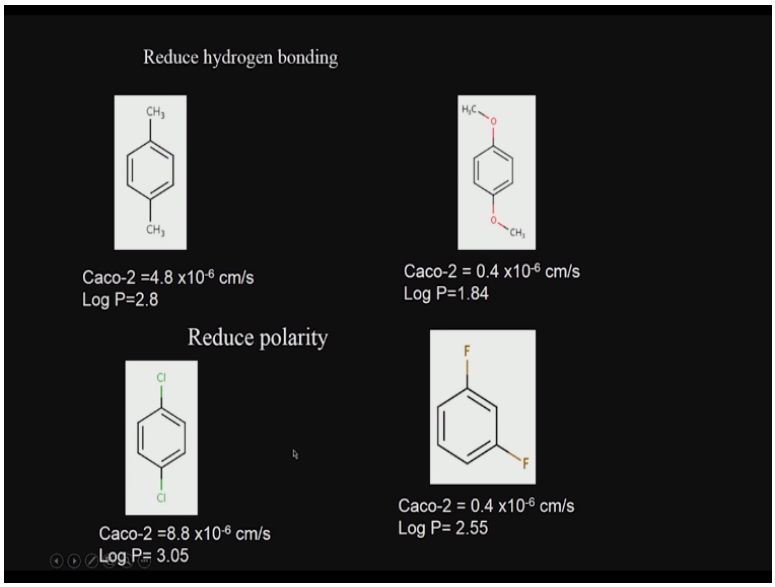

Reduce hydrogen bonding okay, so we have groups, look at this particular molecule, it has got O-CH3-O-CH3 so obviously these are hydrogen bond acceptors. The permeability is 0.4 10 to the power -6. If we remove that permeability has increased dramatically. Reduce polarity, so look at this. So Caco-2 permeability with fluorine groups, 0.4 Caco-2 permeability with chlorine groups it has become 8.8, it is a big 20 times increase okay.

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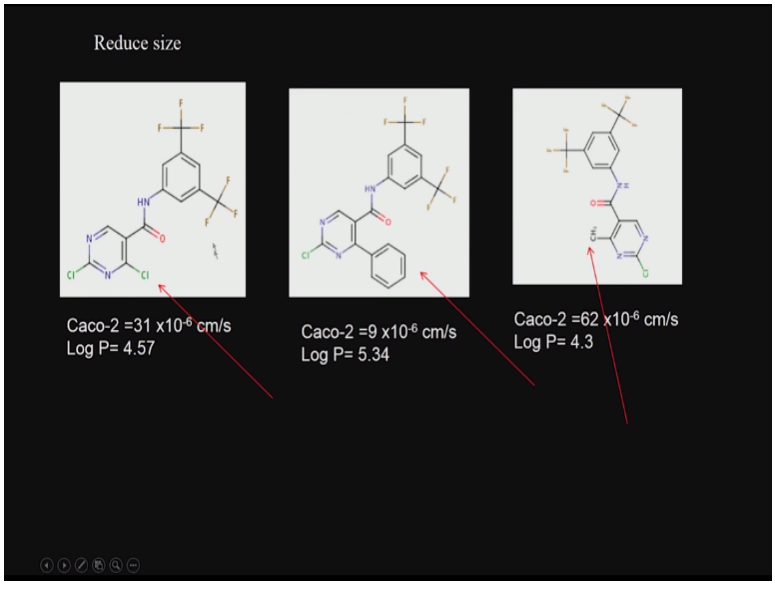

Reduce size, there is a huge molecule, look at this molecule so from 31 10 power -6, 9 10 power -6, 62 10 power -6 by having look at these groups okay. So we can reduce sizes and increase the permeability through Caco understand.

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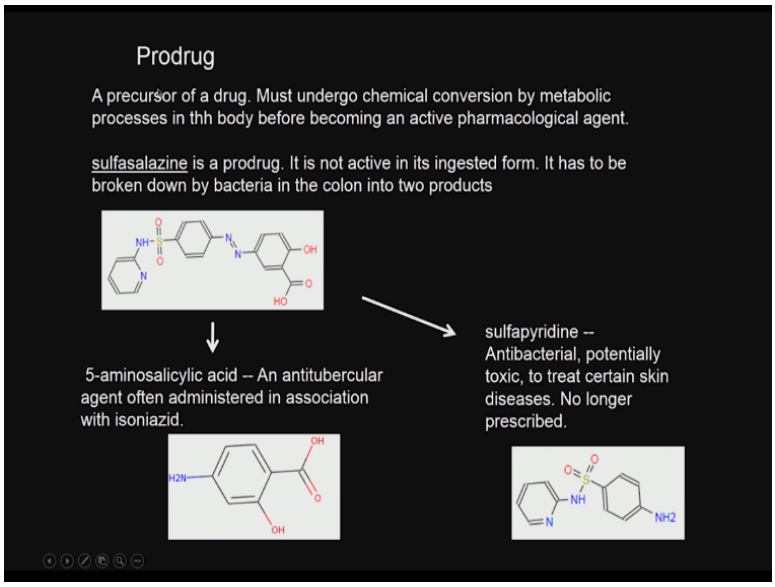

Make a prodrug out of it, what is this prodrug? This is a precursor of a drug and it has to undergo a chemical conversion by metabolic process inside the body, during that process the drug gets released that is the active pharmacological agent gets released that is what is called a prodrug. So the prodrug itself is not active but inside the body because of the presence of enzyme so you may have ester groups or amide groups.

So that particular prodrug gets metabolized, so the drug gets released and then it starts acting okay that is called a prodrug. So you do a prodrug so that there is a good permeability of that whereas the drug itself might not have good permeability because it may be very polar, hydrophilic in nature. Look at this, sulfasalazine, this is a prodrug in its ingested form, it has to be broken down by a bacteria in the colon into 2 products okay.

So this is a particular compound, it is a prodrug, so it is broken down, sulfapyridine, you have the sulphur group, sulphur dioxide pyridine. This is an antibacterial to treat certain skin diseases okay whereas this one is a 5-amionsalicylic acid. We can see the salicylic acid and antitubercular agent of an administered in association with isoniazid, so look at this so this has no activity at all.

But when it is broken, this portion is the sulfapyridine and this portion is 5-aminosalicylic acid so this portion has got antitubercular activity, this portion has got antibacterial activity, but together they do not exhibit any activity. So there is inside the body this particular bond may get broken that is called a prodrug.

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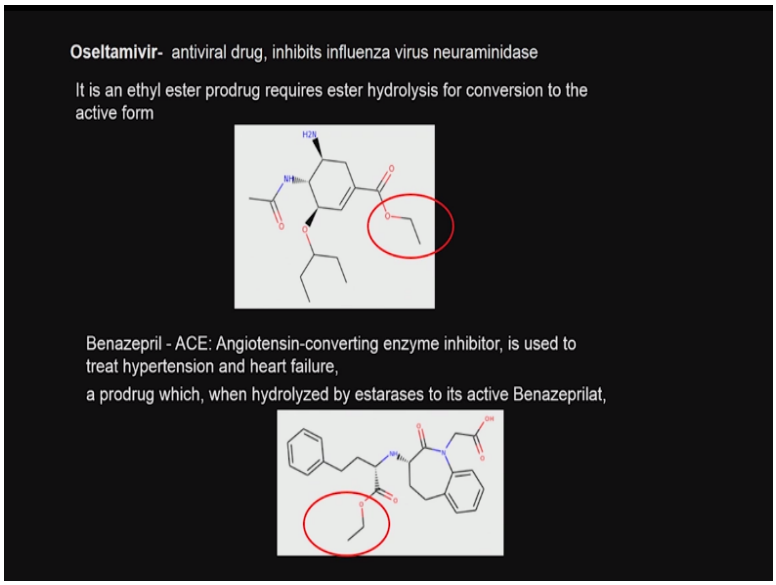

Look at this, this is Oseltamivir, this is an antiviral drug, it inhibits influence of virus neuraminidase, it is an ester so this particular bond has to be broken by hydrolysis so if you have an enzyme inside esterase like it breaks this and then the remaining portion becomes an active material inside okay. This is a prodrug. Benazepril, this is called angiotensin-converting enzyme inhibitor okay.

It is used to treat hypertension and heart failure and again this is a prodrug. This ester bond has to be hydrolyzed by an enzyme come esterase to make this drug active. So it is easy to put in an ester group which will anyway break inside the body because our body contains esterase enzyme then the active drug starts acting inside the body okay that is the strategy that is generally adopted.

So if you have a drug which does not permeabilize inside the body then what you do is you put a functional group with ester bond and it will generally break inside the body because of the esterase enzymes found and then the active drug gets liberated okay so that this whole system is called a prodrug. The prodrug does not have any activity of its own.

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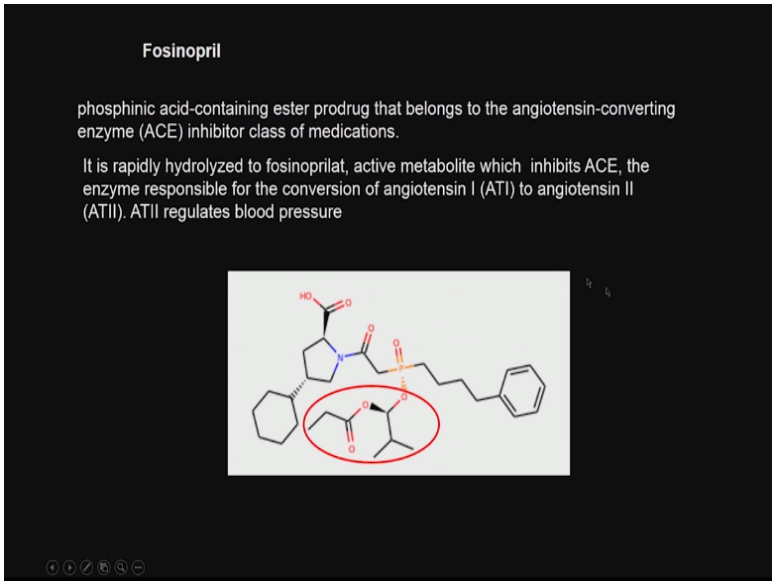

Fosinopril, phosphinic acid-containing ester prodrug okay so it has got a phosphinic acid okay this particular one that belongs to the angiotensin enzyme inhibitor class of medications okay. So this has to be broken. It is rapidly hydrolyzed to fosinoprilat which is the active metabolite which inhibits ACE the enzyme responsible for the conversion of angiotensin I to angiotensin II. ATII regulates blood pressure.

So we do not want too much of ATII in the body and the ATII is produced by the ACE enzyme angiotensin-converting enzyme. So these drugs go and bind to ACE and prevents the formation of the ATII okay. Again this is the prodrug and as you can see these needs to be broken before the drug becomes active.

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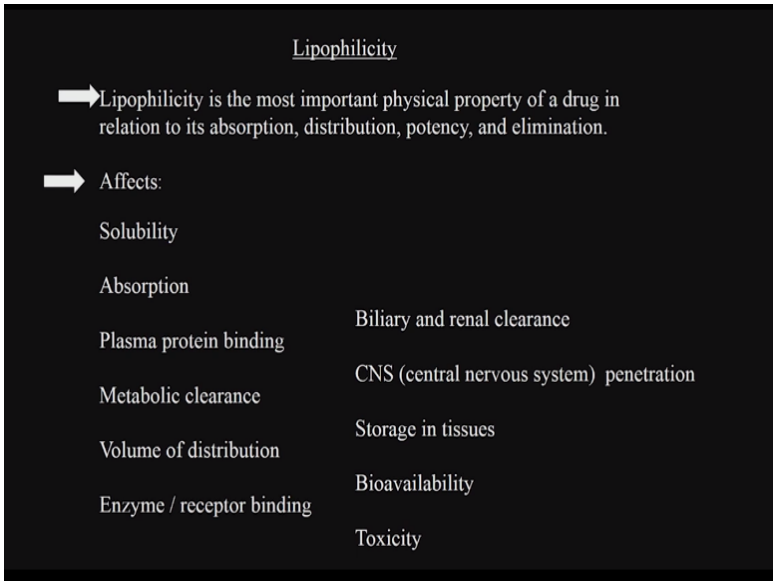

So different approaches we can do, so lipophilicity is the most important physical property of a drug in relation to absorption, distribution, potency, elimination and all that. Solubility, absorption, plasma protein binding, metabolic clearance, volume of distribution, enzyme binding, biliary and renal clearance, central nervous system penetration, storage in tissues, bioavailability, toxicity. So many factors are affected by this lipophilicity okay.

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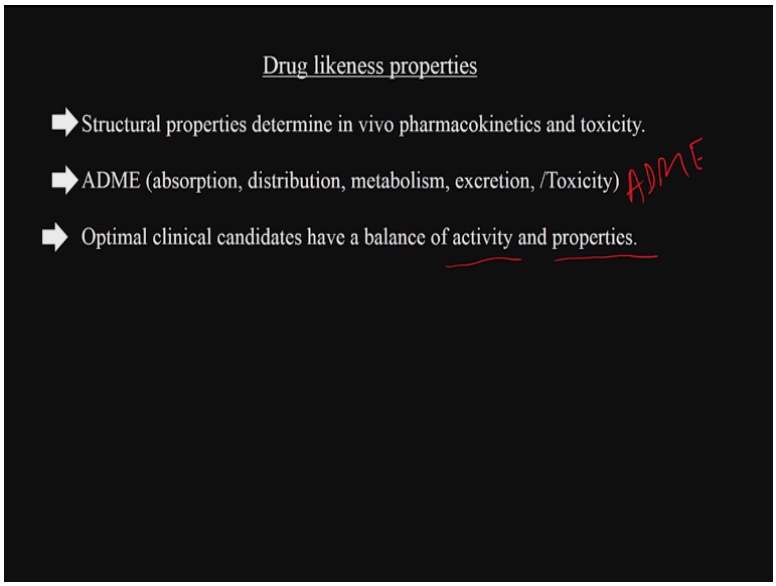

Now we have looked at the concept of solubility, we have looked at the concept of permeability okay. Now there are many other factors and they all come under the class of drug likeness property okay. These are structural properties which determine in vivo pharmacokinetics and toxicity of a compound in the body like ADME A means absorption, D means distribution, M means metabolism, E means excretion and of course nowadays they also include T into this okay that is called T toxicity.

So we can call it ADMET okay, so that is toxicity so if you take optimal clinical candidates they should have a balance between activity and properties that is very, very important activity and properties. So very active material, very poor ADME properties then it cannot pass through the clinical trials, very poor activity is also generally not good so it should have a balance between activity and property.

So we looked at the couple of properties like the solubility, like the penetration or the permeability. There are many other properties like distribution, like metabolism, excretion, toxicity so we are going to look at each one of them in detail because these drug likeness properties determine whether a drug is going to be very good or not so actually okay.

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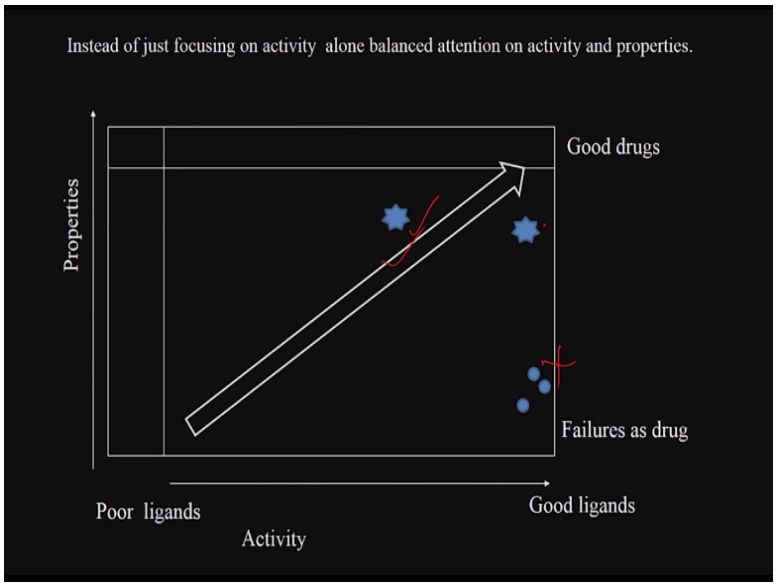

So poor ligands, good ligands so activity increases, poor property, very good property there is so ideally I should have very good properties and good activity. I may have good activity but poor property so these are all failure compounds whereas this could be success I mean this is the most ideal but you may end up somewhere here also so that is also okay that is also okay. This is the most ideal and this is not very good.

So the pharma companies generally look at this region also but getting this is really a big blockbuster but chances are generally you get somewhere here. So you should have reasonably good activity as well as good property for it to have good bioavailability, less toxicity, less side effects and so on actually okay. So we are going to as I said look at all these various other properties in addition to water solubility and permeability through the GI membrane okay.

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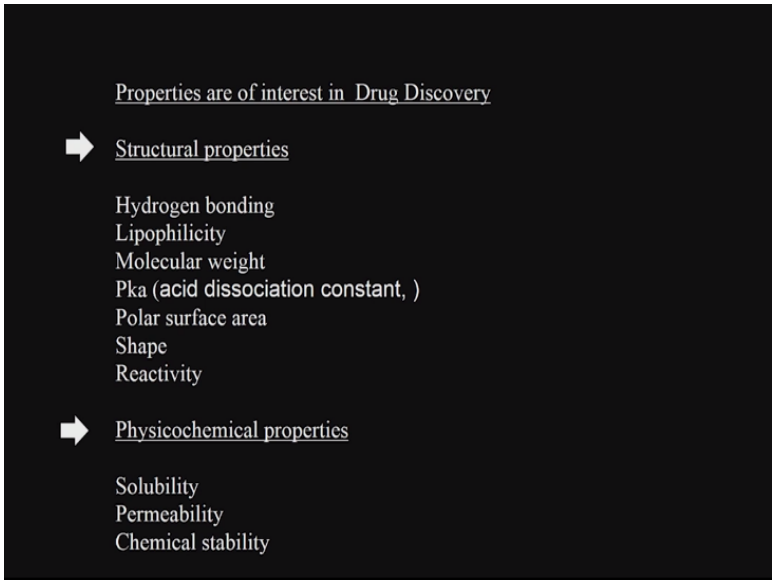

So what are the structural properties, hydrogen bonding, lipophilicity, molecular weight okay, pKa is the acid dissociation constant, polar surface area, shape, reactivity these are the structural properties which affect your solubility, permeability, chemical stability because inside the stomach we are talking pH in terms of 2 so your molecule has to be stable when it goes inside your plasma you are talking about enzymes like esterases, oxidoreductases, lipases.

So your drug has to be still stable in the presence of all these enzymes. So stability also becomes very important, not only different pH conditions but also inside your body.

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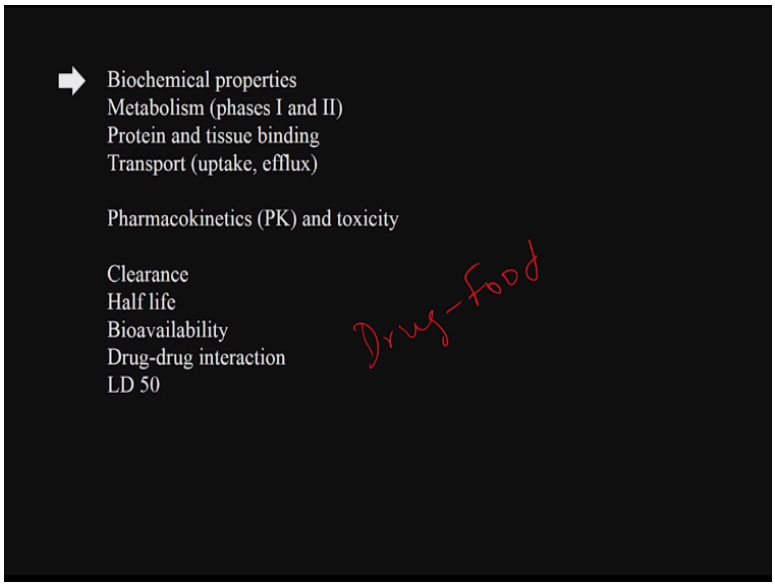

And the biochemical properties are important, metabolism how the drug gets metabolized inside okay, does it bind to the protein inside, does it bind to the tissues inside your body,

how does it get transported, up taken. All those become very important and later on clearance. Drug once it has done its job, it has to come out, get thrown out, excreted so clearance is very, very important.

What is half-life of the drug? That means the concentration in the plasma has come down 50% level than bioavailability. What is the concentration of the drug available at the target site? If you are taking 2 drugs, 3 drugs, is there a drug-drug interaction? And nowadays there is a drug-food interaction also come into the picture because some drugs are not good with some food and some drugs get up regulated in the presence of some food.

So we need to consider this also and then lethal dose. LD 50 is lethal dose to kill 50%, so all these effects also come into the picture when you are designing and they are called the drug likeness property okay.

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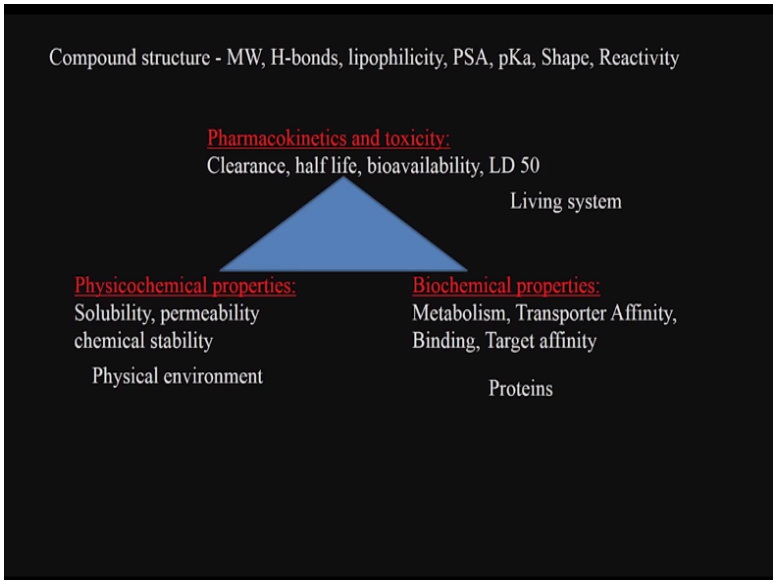

So this is a very interesting slide, we have the pharmacokinetics okay toxicity, the clearance, the half-life, bioavailability, LD 50 on the living system. Then, we have the biochemical properties like metabolism, transporter affinity, binding and then we have the physicochemical properties of the drug solubility, permeability, chemical stability that is the physical environment.

So we have the living system here and then we have the physical environment of the drug and then we have all the protein and all that actually okay, compound structure, what I can change? I can change molecular weight, I can change the hydrogen bond donors and

acceptors, I can change lipophilicity, I can change polar surface area, PSA means polar surface area, pKa that is dissociation, I can change shape, size, reactivity.

So all these I have control on but we have to see how it affects the binding with the target protein okay and then how its toxicity is affecting in living systems, what is its stability inside, what is its excretion inside and half-life and bioavailability okay. So we will continue more on this topic in the next class as well. Thank you very much for your time.