Computer Aided Drug Design
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Lecture - 07
Drug Solubility

Hello everyone, welcome to the course on computer-aided drug design. Today, we will talk about drug solubility. This is a very important parameter because most of the drugs are taken orally and they have to be water soluble but then as the drug reaches the GI tract, goes to the stomach, intestine, the pH in the stomach is extremely low, a value of 2 and then it rises to a value of 4 okay. So the drug has to be soluble at all these pH conditions okay.

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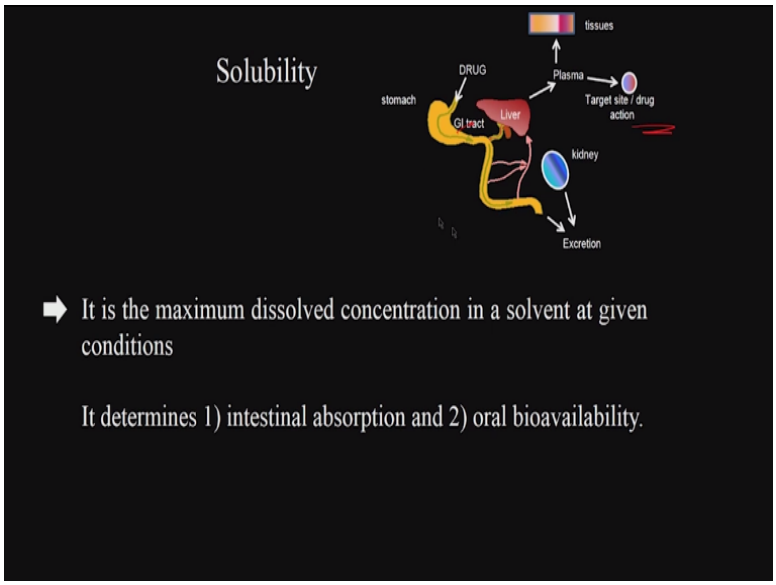

Once that is done the drug goes into the blood stream where the pH is 7.4. Again, the drug has to be soluble okay so drug has to be soluble at all these conditions and hence solubility plays a very important role in determining its bioavailability, efficacy, dosing strategy and so many parameters okay. So what is the definition of solubility? It is the maximum dissolved concentration in a solvent at a given condition that means temperature and so on okay.

So it determines the intestinal absorption so if the drug is not soluble it remains as a solid so it may get effluxed out through the GI tract okay and it also determines the oral bioavailability because whatever goes inside okay has to come on the other side to the target site hence the oral bioavailability is also determined by the drug solubility.

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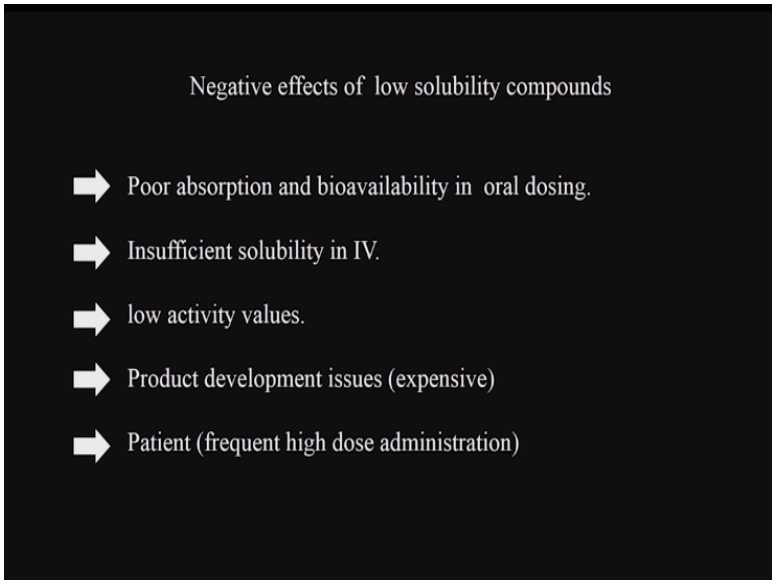

So poor absorption and poor bioavailability are big problems because of poor solubility. Insufficient solubility in IV because even the drug is given intravenous it cannot be in a solid form, it has to be completely dissolved. It will exhibit low activity because solubility is low so whereas in my lab it may work well but when it goes through the GI because of poor solubility activity may look very low.

The product development becomes a big issue okay so it becomes very expensive. How do I make the drug more soluble? So we may have to think about a novel drug delivery system and so on and then for the patient it becomes a big issue because patient has to take the drug quite often because the bioavailability is poor, the absorption is poor so for the patient also it is a big problem.

So solubility plays a very important role that is the starting of the journey of the drug from the mouth or the oral cavity before it reaches the target site okay.

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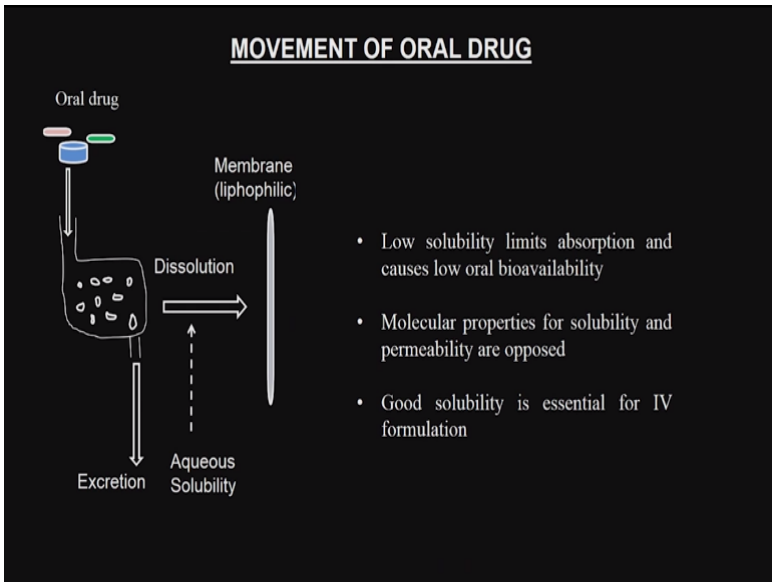

So let us look at this, of course you take oral drug, it goes into the stomach, it has to completely dissolve here and that is dissolution happens that means aqueous solubility plays a very important role and then it crosses the membrane the lipid membrane before it reaches the blood. So whatever does not dissolve will slowly go down through the GI and if it does not dissolve even at pH 4 and so on it may get excreted.

So low solubility limits absorption and cause low oral bioavailability and of course solubility and permeability are opposed to each other okay in molecular properties and good solubility is essential for intravenous dosing because as I said before when the drug is injected as an intravenous it cannot be in a solid form. It has to be completely in a dissolved form.

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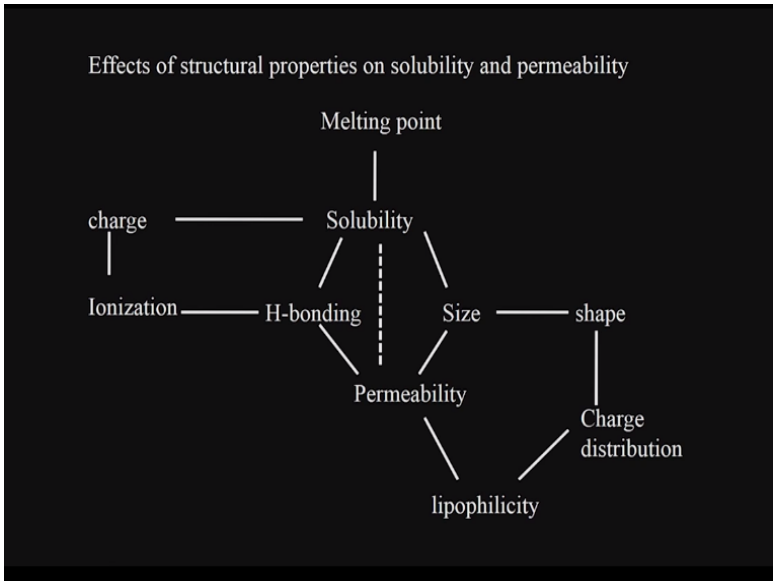

So there are many parameters of the drug or many structural properties of the drug or structural features of the drug that determines solubility and permeability okay. Solubility is the first step where the drug gets completely dissolved in the stomach fluid and then it crosses the lipid barrier and permeabilizes and reaches the blood stream okay. So many parameters matter so we are going to look at some of them as we go along.

The size matters okay, the shape matters okay. Size is also going to affect permeability because very large molecular weight may not get permeabilized. Then the charge distribution of the molecule okay, so if the charge distribution if it is very charged of course it will be more polar, so it will be less lipophilic, it may not get permeabilize but it may have good solubility.

Because charge, ionization all these determine solubility that is why solubility and permeability are sort of opposing. If I have a drug salt form, drug is highly soluble because as you know salts are highly soluble but if it is a salt form it may have polarity so it may be difficult for the drug to cross the lipophilic membrane and reach the blood stream so obviously solubility and permeability are opposing each other here.

So hydrogen bonding, ionization, charge, all these determine solubility because if it is highly hydrogen bonded then solubility is very poor, if it is ionized of course solubility is good, if it is charged also solubility is good. Melting point also determines the solubility because melting point has relationship with crystalized form of the drug and so on. Amorphous material is more soluble than crystalized material.

So you sometimes try to make the drug more amorphous and so on actually. So solubility and permeability are sort of opposing each other and we are going to see that in the next few lectures okay.

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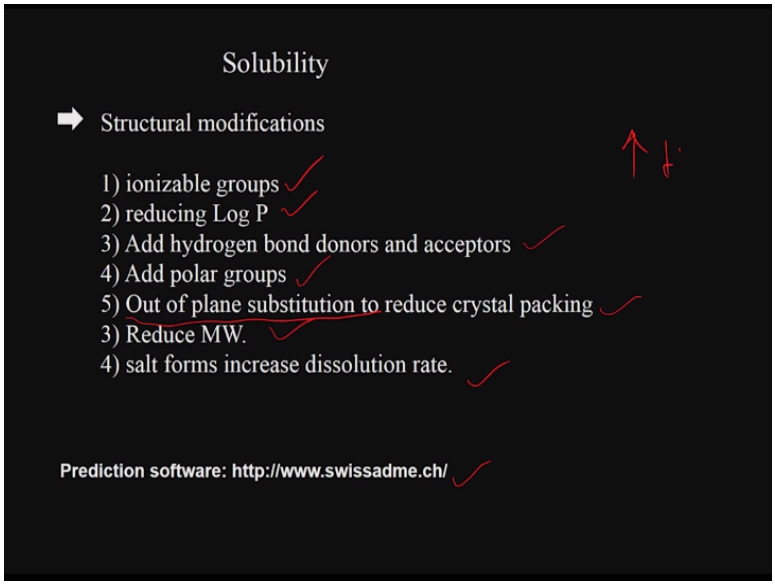

Solubility, you can do lot of structural modifications to improve solubility. We can put in ionizable groups okay as I said salts are always highly soluble that is why 70% of the drugs are in salt form. Reducing Log P, Log P we are going to spend more time in the subsequent slides, it determines the hydrophilic, hydrophobic balance. So if the Log P is high that means it is hydrophobic.

If the Log P is low that means it is hydrophilic that means higher hydrophobic and lower, it is hydrophilic okay hydrophilic and so on and we will look at in more detail later. Adding hydrogen bond donors and acceptors okay that is structural modifications and that is another thing we can do. Add polar groups that means we can have different types of oxygen and nitrogen there.

We can have out of plane substitution to reduce crystal packing because crystals as you know are packed structures and highly crystalline materials are poorly soluble so you break the crystallization by introducing out of plane substitution. Then reduce molecular weight, if the molecular weight is very small and the drug is soluble, large molecular materials are not soluble.

Salt forms increases dissolution rate. As I showed you last time this particular software SwissADME predicts what is the solubility of structures. We can draw some structures and then we can say this is the solubility, it is a predictive tool using certain regression relationship okay we are going to look at some of these techniques by which structural modifications can improve solubility okay.

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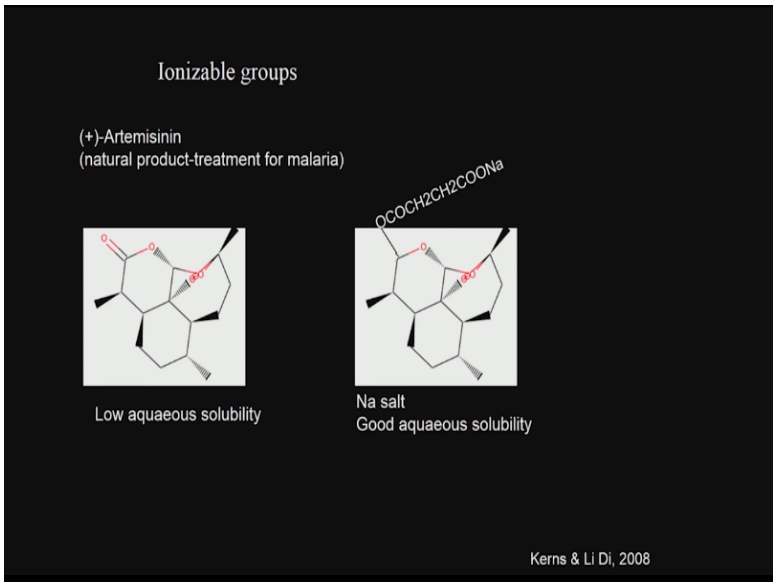

Let us look at this ionizable group, this is called Artemisinin, this is a natural product which treatment for malaria, it has got a very poor aqueous solubility okay, you can see lot of hydrophobic groups, CH3-CH2-CH2-CH2 of course it has got some oxygen but predominantly lot of hydrophobic group okay so what they do? They add a sodium salt here so the solubility improves.

It is good aqueous solubility because of the sodium salt. This happens in Taxol. Taxol is an anti-cancer drug and it has got extremely poor solubility and bioavailability so when you make a salt format the solubility increases almost double.

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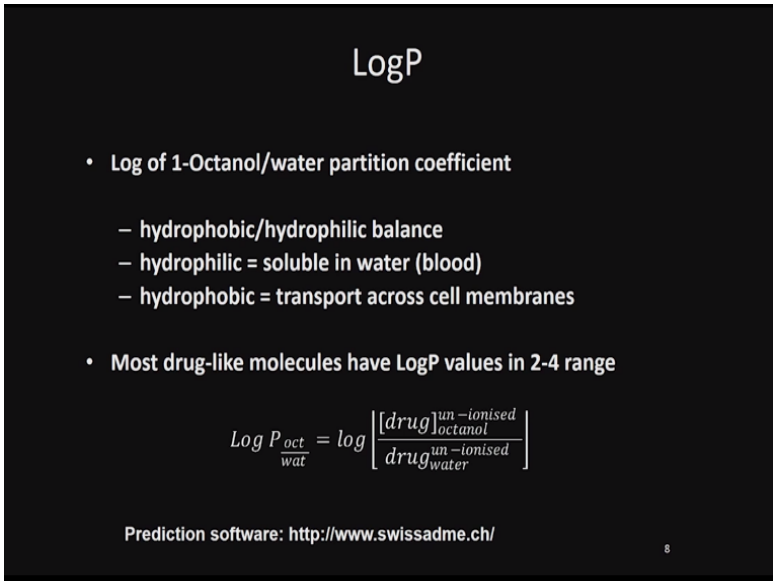

And now let us talk about Log P. This is a very important thing which you will be coming across so I will spend some time on this. Log P is the ratio of Octanol to water partition coefficient. So if you take a drug and take a mixture of Octanol and water, drug will partition between Octanol and water. Water is aqueous so hydrophilic, Octanol is lipophilic okay hydrophobic.

So if more drug is there in Octanol that means the drug is hydrophobic, if more drug is in water that means it is hydrophilic okay so the Log P tells you the hydrophobic and hydrophilic balance okay because Octanol water so hydrophobic hydrophilic balance. Hydrophilic water soluble or in blood soluble, hydrophobic transport across the cell membrane.

As you can see Log P is going to be contradicting between solubility and permeability okay if the Log P is very high that means it is hydrophobic, it will pass through the lipid membrane but solubility can be poor. If the Log P is low that means it is hydrophilic that means it will be highly water soluble but passing through the membrane maybe difficult. So most of the drug like molecules will have a Log P of 2 to 4.

So you take a balance, 2 is hydrophilic, 4 is hydrophobic but it is neither too much of this or too much of that okay that is the beauty of it. So how do you estimate Log P? You take logarithm and see a drug in Octanol/drug in water okay. Again, SwissADME if you go to that software you can draw structures and we can predict what will be the Log P of a particular structure okay.

So if the Log P is very low below 2, then you may feel that it is going to be hydrophilic so it is better to reduce the hydrophilicity. If the Log P is above 4 for example some of the antifungal drugs have very high Log P, they are highly hydrophobic and so you may have to think about making it more hydrophilic. So generally if you have a molecule, you are testing it and if you feel the Log P is not in this range so be careful, it may have poor solubility or bioavailability and so on okay.

So this equation is valid for un-ionized material okay, un-ionised compounds.

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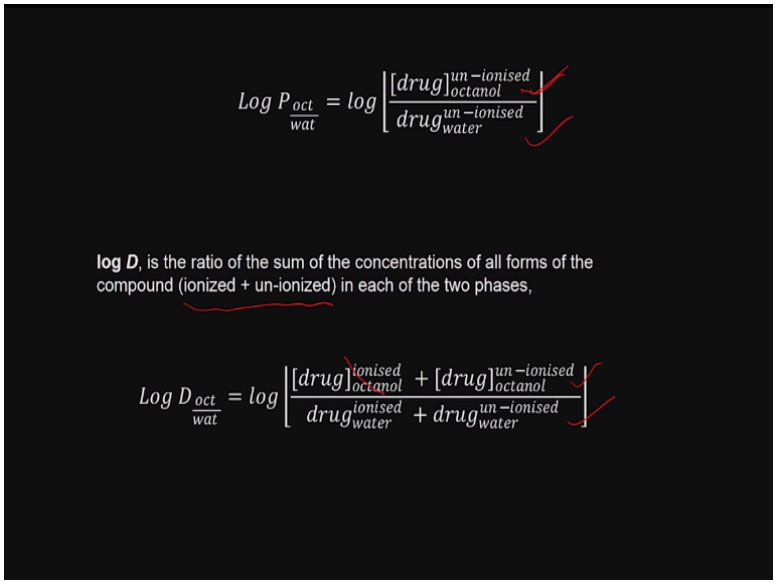

There is another term called Log D that is for ionised okay. It considers concentration in all forms, compounds in ionised form, compounds in un-ionised form and so on actually. So it takes ionised, un-ionized and of course you will not find suppose you have a solvent you might have very little or practically zero ionized form whereas in aqueous polar compounds, salts will get ionized okay.

So the Log P is logarithm of drug in the Octanol/logarithm of drug in the water whereas Log D we will take drug in ionised in Octanol drug un-ionised in Octanol/drug ionised in water drug un-ionised in water. As I said if you have a solvent like chloroform, you are not going to have ionisation so this term will become practically zero so you will have a drug in 2 forms, ionised and un-ionised only in the aqueous form but in the solvent you will not have that.

So this is called Log P and this is called Log D. There are different ways of calculating Log P. There are many different softwares, which calculate Log P based on some regression relationship. So you may get different answers depending upon the type of softwares you use okay. There will be lot of difference because each software will select say 1000 compounds from the literature whose Log P is known or experimentally determined.

And then they will develop a regression relationship. So if I use software 1 and software 2, I may get different values of Log P and some softwares use something called group contribution method. That means a OH group contributes certain amount towards Log P more towards hydrophilic whereas a CH3 group may contribute more towards hydrophobic so that is called a group contribution method.

So they calculate Log P based on that so you get different values for Log P depending upon the type of software we use and similarly we get different values for Log D depending upon the type of softwares we use. So Log P is the un-ionised form whereas Log D is the ionised form and generally only in the aqueous we find the ionised and un-ionised whereas if we take a solvent like chloroform you will not find the ionised form.

So we will have only one term in the numerator if you are calculating Log D. So experimentally how do I calculate Log P? I take a mixture of Octanol and water okay and then I put the drug inside and then I shake it nicely okay I take a drug Octanol in water then I shake it nicely and then I see how much of the drug is in the Octanol layer okay, how much of the drug in the water layer and then I take a ratio, I take the logarithm okay.

So whatever amount of drug in the Octanol we consider it to be hydrophobic and whatever drug in the water layer we consider hydrophilic. So that balance is called the Log P okay.

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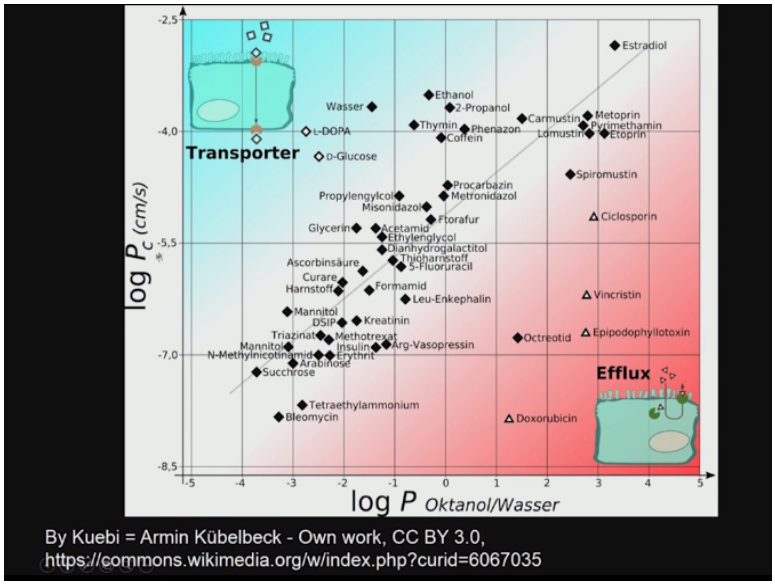

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So Log P also plays a very important role as I said in the permeability or the diffusion so this is the data which was taken from this reference okay so we have to acknowledge this. So as the Log P increases as I said it becomes very hydrophobic. So it is easy for it to penetrate the barrier so diffusion or permeability is also very high.

As the Log P is very low, it is very hydrophilic so the permeability that is it transport logarithm of centimeter per second is also very, very low. So they have drawn a sort of a

linear relationship here okay so drugs which have very high Log P will also have very high diffusion through that. Of course this graph does not talk about solubility part but it talks only about the permeability or the diffusion into that okay.

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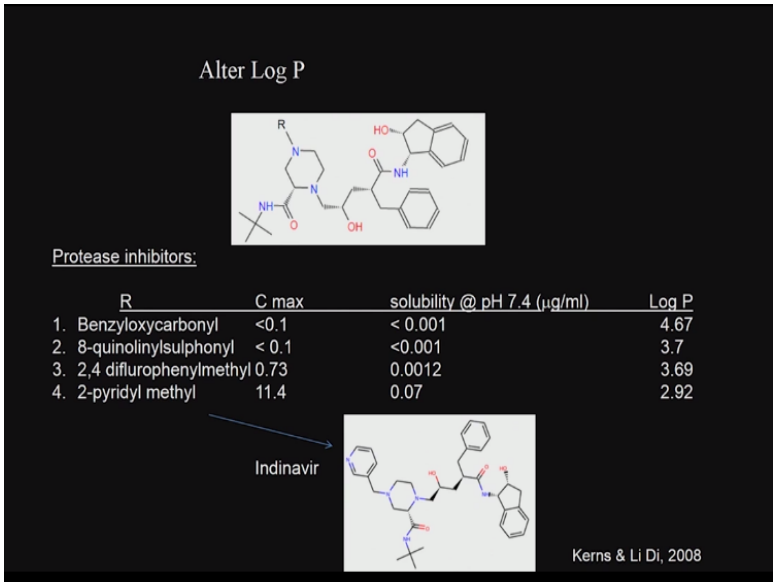

So Log P if I can alter Log P to improve its solubility okay so make it more hydrophilic. For example, these are protease inhibitors okay, these are called protease inhibitors and their R group is there on nitrogen so as you can see different R groups benzyloxycarbonyl, 8-quinolinylsulphonyl, 2, 4 diflurophenylmethyl, 2-pyridyl methyl okay so different R groups. So Log P keeps going down as you can see 4.67, 3.7, 3.69, 2.98 and the solubility has gone up tremendously almost more than 700 times you can see at 7.4 that is in the blood.

This is Indinavir protease inhibitor, this is taken from this particular reference which is very interesting so as we keep changing R group here and make it more hydrophilic or reduce the Log P from this value to write down to this value, the solubility also increases as you can see from 0.001 microgram per ml at plasma to 0.07 so a big increase, so altering Log P or making it hydrophilic will improve.

Of course, it may affect the permeability, we are not talking about that but we are just looking at solubility. That is why in drug discovery many parameters or features are going to be contradicting each other. It is not just we change one and achieve your goal. When you change one and make it favorable something else could become unfavorable as you can see in this particular example.

The Log P decreases so the solubility increases but we do not know about the permeability of this particular change okay.

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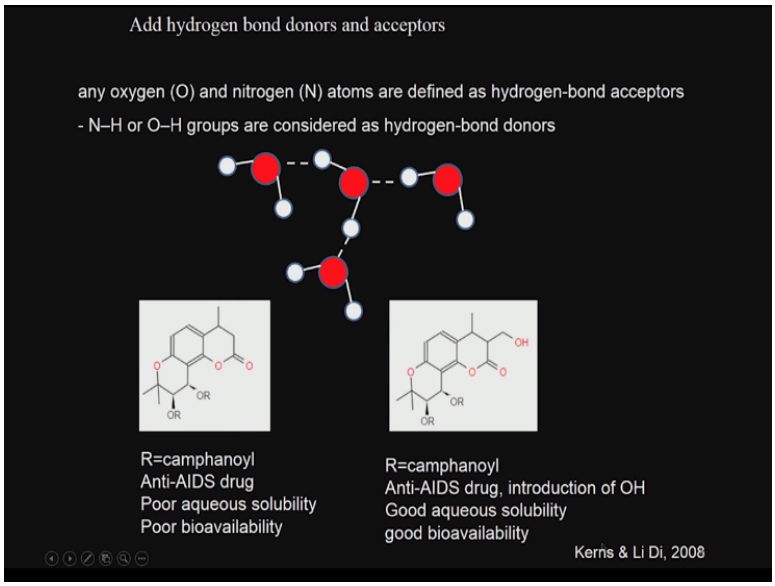

Hydrogen bond donors and acceptors, by adding hydrogen bond donors and acceptors we can change the aqueous solubility. For example, what is a hydrogen bond? Donor or acceptor? Oxygen, nitrogen is defined as hydrogen bond acceptors okay whereas N-H or O-H groups are considered as hydrogen bond donors. Of course, in acidic O-H will become O- and H+ then that is not a hydrogen bond donor please remember that.

But if you take water in this particular example okay water is there you have the oxygen, hydrogen, hydrogen so the oxygen here becomes an acceptor whereas these O-H and O-H become donor actually so it has got 3 things happening, it is accepting as well as donating. So look at this drug, this is an anti-AIDS drug. There is an R group here, R is camphanoyl. It has got poor aqueous solubility, poor bioavailability.

So introduction of OH here, look at this, we have introduced OH. So what happens, it can have hydrogen bond donor okay then aqueous solubility increases, the bioavailability also increases, very interesting again this was taken from this particular reference.

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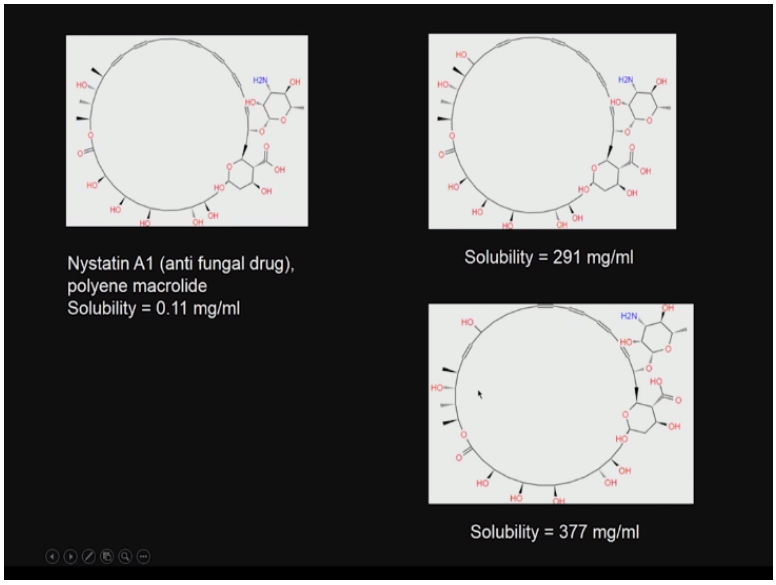

Look at these drugs. These are all antifungal drugs as originally I said antifungal drugs always have poor solubility. Look at this, this is called a polyene macrolide, it is a huge structure so it is called a macrolide. The solubility is 0.11 milligram per ml. As you can see here, the solubility is 291 milligram per ml okay and then look at this solubility has become 377 milligrams per ml.

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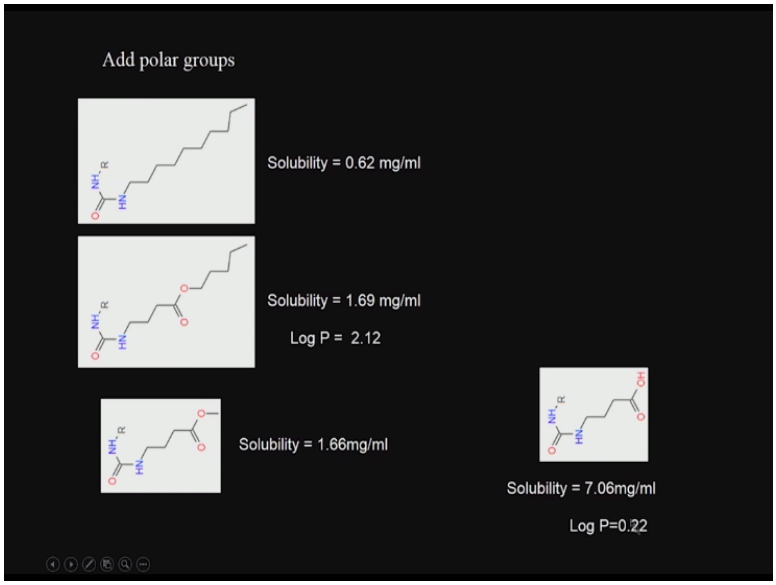

Add polar groups okay, so we can add polar groups that means we can add oxygen's and nitrogen's. Look at this molecule, it has got 1 oxygen, 2 nitrogens okay, solubility is 0.62. Now they have added oxygen's here and here, solubility becomes 1.69. Look at this molecule okay, some of the CH2 groups have been removed, solubility has become 1.66 and now make an acid out of this solubility has gone to 7.

So we have almost increased the solubility by 10 times here. Log P here is 2.12, here it is 0.22 because we have removed lot of CH2 groups, which are hydrophobic that is why Log P has gone down. So Log P has gone down, solubility has increased, so we have added more polar groups.

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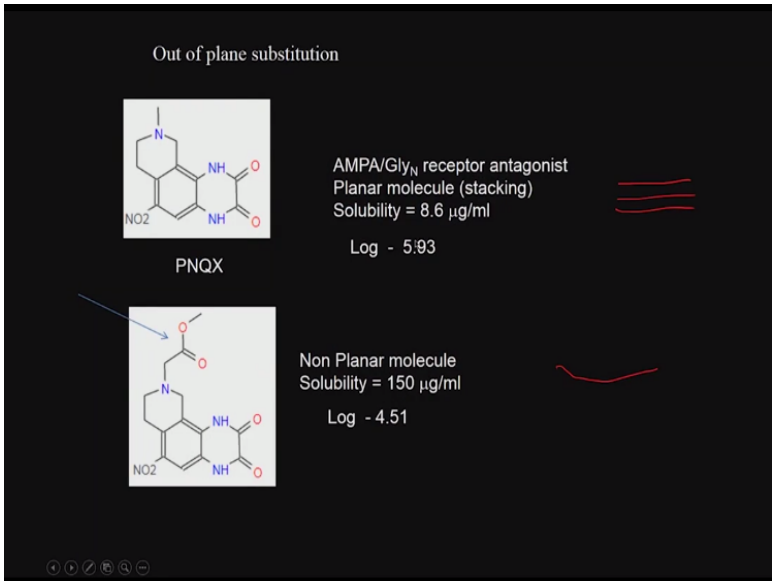

Out of plane substitution, if a structure is well packed, very crystalline, solubility is very poor. Look at this structure. It is a single plane because we have diffused rings so they will be planar, planar, planar like this. So it is highly crystalline in nature. So the solubility is extremely poor. Planar molecule they have stacked. This is AMPA/Glycine N receptor antagonist.

Now all you do is you add an acetyl group here, so what happens, no more it is a plane. Because of this what happens, the molecule is not a flat structure but it has got structure like this okay so because of the acetyl groups. Because of the acetyl groups the molecule is like this so it becomes non planar so solubility has become little amorphous so solubility has increased to 150 microgram, it is a big increase that is called out of plane.

So any crystalline material if you make it into amorphous material, solubility is increased. This is one way of structural modification; sometimes they add another material which prevents the crystallization of the parent compound of the drug so that the drug becomes amorphous. There are many examples where when we make the formulation of the drug, they add another compound which will prevent the crystallization and hence the formation of crystal structure okay.

So again the Log P there is a difference in this -5.93 to 4.51 okay.

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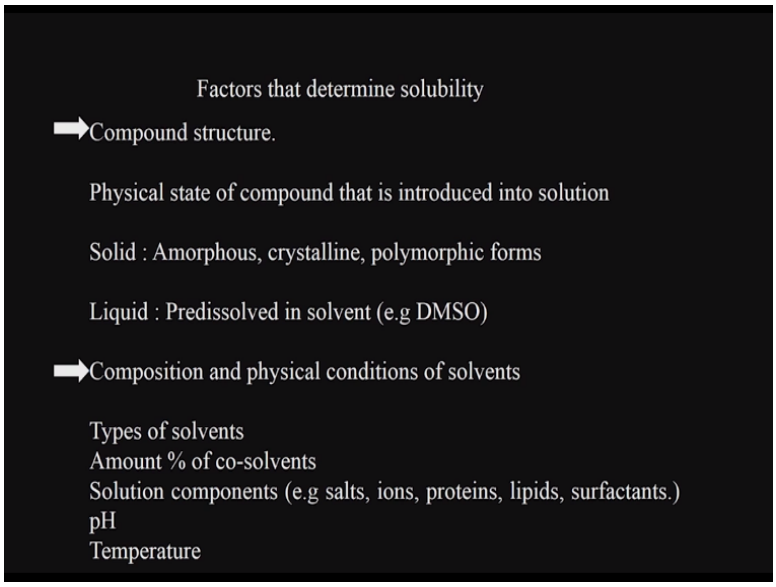

So factors physical state of the compound okay solid amorphous, crystalline, polymorphic so more amorphous it is that is going to be more soluble, predissolved in solvent so if it is in a liquid form composition and physical conditions of solvent, type of solvents sometimes they add also co-solvents to improve solubility especially in IV formulation, salts, ions, proteins, lipids, surfactants.

Surfactants can also make it more soluble, pH modify the pH conditions to make it soluble. Temperature, I can change the temperature, of course when we talk about the oral drug we will not be able to talk about change in temperature okay.

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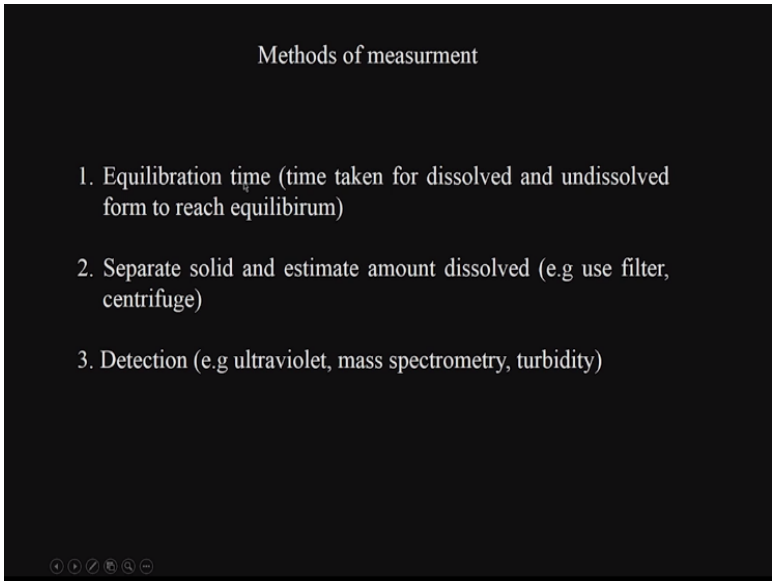

So there are many tools for measuring solubility. One is called equilibration time that is time taken for dissolved and undissolved from to reach equilibrium. So what I do is I take a solid drug, put it in the solvent or water and then I will see how long it takes for it to reach equilibrium for the solid and the dissolved form. Then separate solid and estimate amount dissolved okay by using a filter paper or a centrifuge.

I can use detect how much has been dissolved using ultraviolet, mass spec, turbidity. These are some methods, which are approved by FDA for determining solubility and all these are very, very important not only the amount that is dissolved but also how long it takes for the material to dissolve okay.

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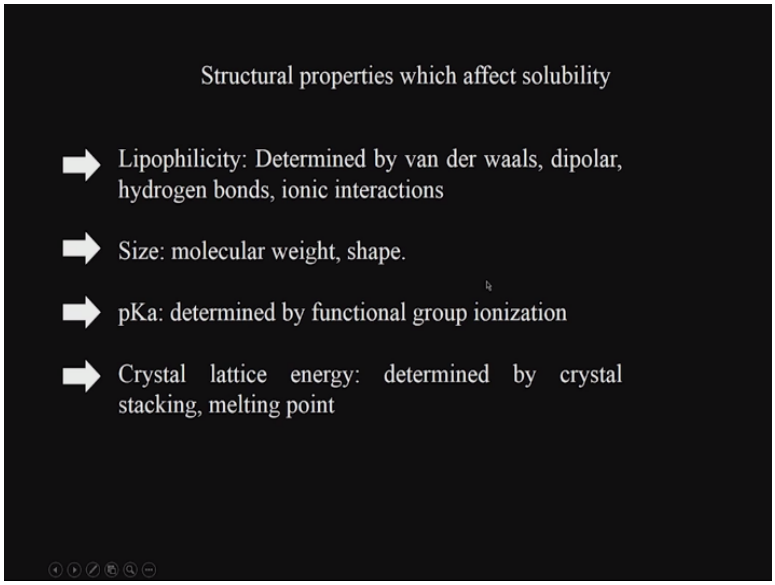

So we looked at many structural properties, lipophilicity which affects solubility. So lipophilicity is determined by Van der Waals, dipolar hydrogen bonds, ionic interactions. Size, molecular weight, shape. pKa, pKa is nothing but dissociation constant, pKa is also determined by the functional group, what type of ionizable group proper, crystal energy that is crystal stacking, melting point, all these also affect the solubility okay.

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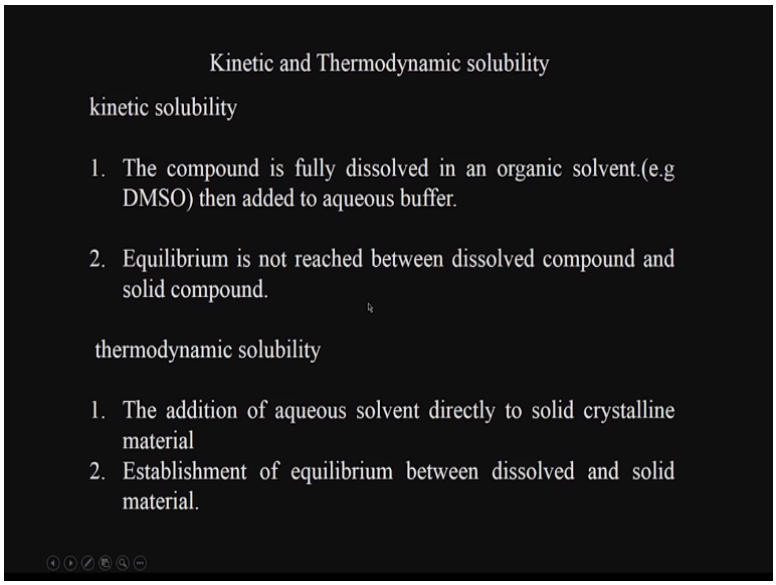

Let us look at the kinetics and thermodynamic solubility. What is this kinetic solubility? The compound is fully dissolved in an organic solvent then added to aqueous buffer. Equilibrium is not reached between the dissolved compound and the solid compound okay, this is called the kinetic solubility that means you dissolve it completely and then you are then taking it into another solvent, so the solubility changes okay.

Thermodynamic, the addition of an aqueous solvent directly to solid crystalline material and then establishment of equilibrium between dissolved and solid material. This is thermodynamic solubility, other is kinetic solubility. Thermodynamic solubility is the reaching of equilibrium between the dissolved and the undissolved whereas in kinetic it is in dissolved form okay.

Then you transfer it into another solvent, so equilibration is not reached between this dissolved compound and the solid compound okay and that is what is called kinetic solubility okay. For example, I take a drug orally and the drug goes to the stomach and then the stomach empties so the time is fixed, within that time the drug has to dissolve that is why kinetic solubility plays an important role.

Thermodynamic solubility is the if the drug remains to stomach for a very, very long time without the problem of empting of the stomach contents then it will always reach an equilibrium and that is called thermodynamics solubility. That is the ultimate solubility.

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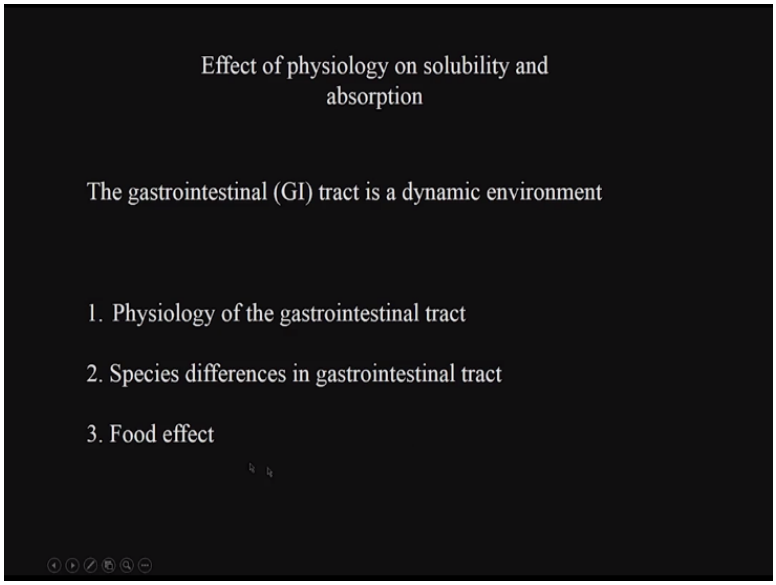

So physiology on solubility, the gastrointestinal tract is a dynamic environment because food comes in, water comes in and then after certain time the enzymes play an important role and there is an emptying so physiology of the intestinal tract, species differences in gastrointestinal tract that means one person may have different set of bacteria, another person may have different set of bacteria.

Food, what type of food we are eating, all these also play a very important role. Of course, we do not have much control but as a medicinal chemist we do not have much control on this but these also matter a lot okay.

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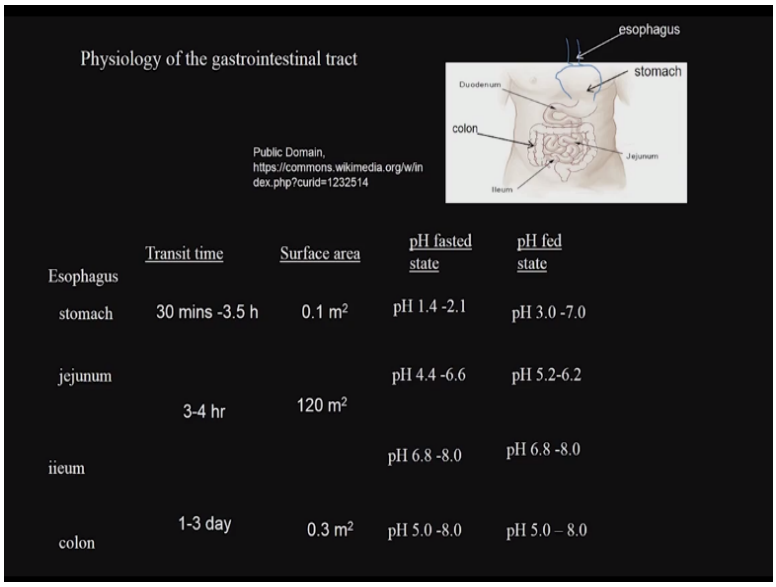

So if you look at the physiology of the gastrointestinal tract, this was taken from a public domain okay. We have the stomach then this is colon, this is called the duodenum okay. This is called the jejunum okay, then this is called the ileum okay. So the food comes to esophagus, then stomach, then duodenum, then it comes to jejunum and then colon, descending colon and so on actually.

Now the surface area of each of these regions are very different, the pH of each of these regions are very different and the pH changes depending upon whether food is avail inside or not okay. So for example if you look at the esophagus in stomach, transit time in esophagus could be very fast 30 minutes, then it goes to 3.5 hours. The surface area is 0.1-meter square, pH is very, very low 1.4 to 2.

When it is fully fed, it could go up to 3 to 7. Now if you look at jejunum here that is we call it small intestine, 3 to 4 hours, look at the surface area tremendous 120 meter square and then the pH is higher 4.4, 6.6 and then fed 5.2, 6.2 if you look at the ileum here pH is 6.8 to 8 okay so the surface area of the small intestine jejunum is very, very large. So we can expect lot of drug absorption in this region when compared to say stomach and pH is also very low in the stomach.

Now if you go to colon, here the transit time is 1 to 3 days, the surface area is 0.3-meter square, it has gone down tremendously, pH is also high 5 to 8 okay. So each of these regions are very different, the transit times are very different, the pH conditions are different and if

you see the stomach pH can change from very acidic to almost higher values depending upon whether it is fasted or un fasted.

So the drug absorption can be very different in each region. So if I want a fast acting drug, I want it to dissolve say in stomach. If I want a normal drug, I want it to dissolve in the small intestine. So the drug absorption can change, the drug action can change and so on actually. So we need to understand the physiology of the stomach to understand the solubility and hence drug action.

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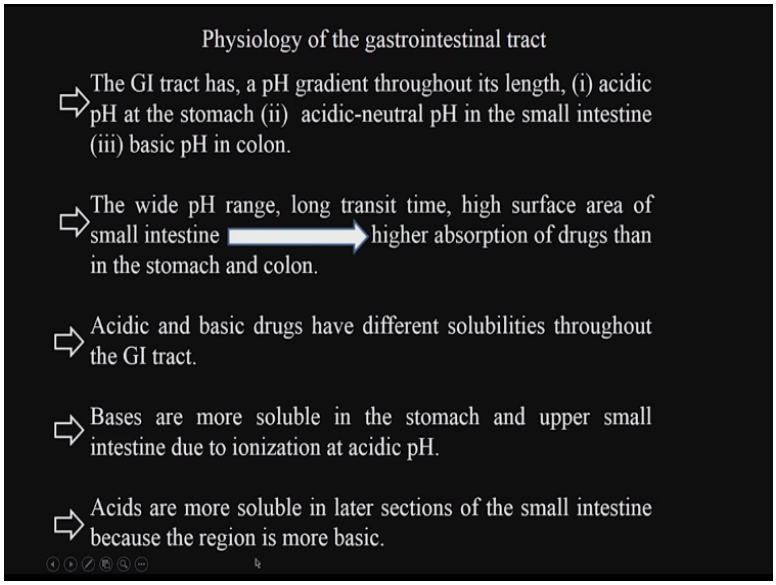

So physiology of the gastrointestinal, GI has a pH gradient throughout its length as you can see starting from 1 right up to 5 or 6, acidic pH of the stomach, acidic neutral in the small intestine, basic in the colon. This wide range of pH, long transit time, high surface area of small intestine, so most of the drug should get higher absorption of drugs than in the stomach and colon.

Acidic and basic drugs have different solubilities throughout the GI tract. As you can see, acidic drugs that is pKa is acidic, basic drugs pKa is basic. So they will have different solubilities in the stomach. Bases are more soluble in the stomach and upper small intestine due to ionization at acidic pH. So if the drug gets ionized, it will not go through the lipid because they are very polar.

If the bases will not get ionized so it will travel through, so bases are soluble in the stomach. Acids are more soluble in the later section of the small intestine because the region is more basic okay.

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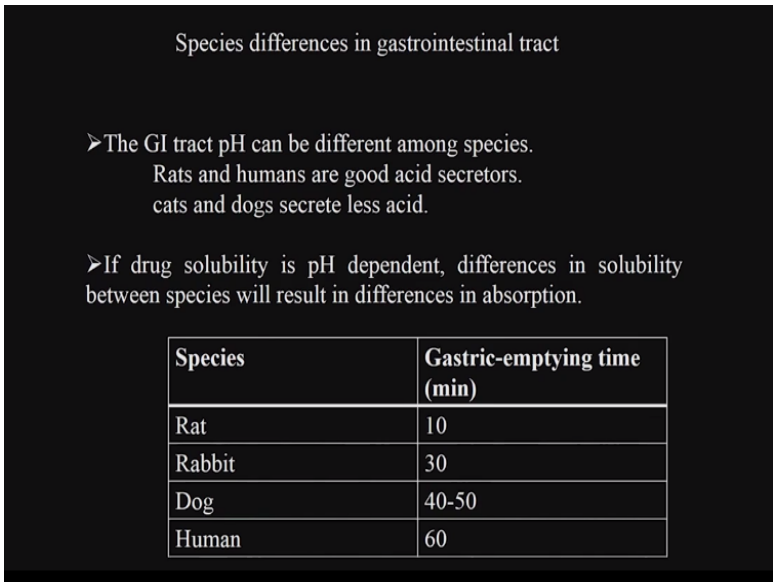

So GI tract pH can be different among species, Rats and humans are good acid secretors. Cats and dogs secrete less acid so if the drug solubility is pH dependent differences in solubility between species will result in different absorption so rat you will get pH changes. So the gastric emptying time is 10 minutes, rabbit 30 minutes, dog is 40 to 50 minutes, human 60 minutes.

So you see a large difference, so obviously there could be differences in the performance of drug because of the emptying of the drug between various species and when I am doing a clinical trial with animals, the results can get modified because the emptying times are also very different okay. So we will continue on this solubility and drug permeability in the next class as well. Thank you very much for your time.