Rate Processes

Prof. M. Halder

Department of Chemistry

Indian Institute of Technology, Kharagpur

Module No. # 01

Lecture No. # 16

Enzyme Inhibition

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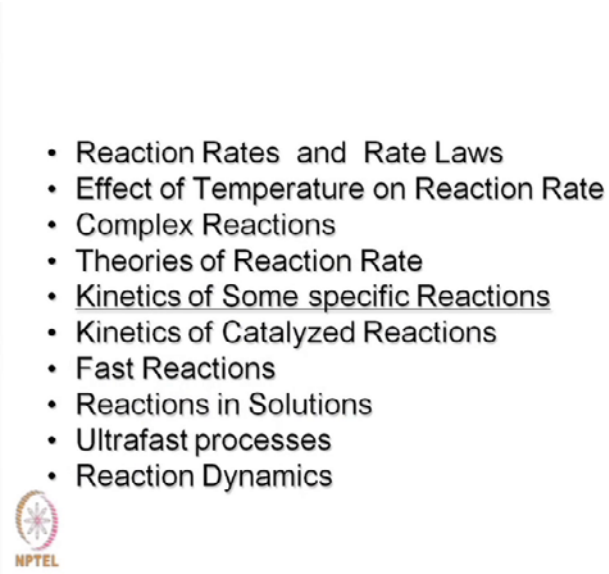

Hello welcome back to our lecture series in rate processes. So today, we will take up this topic on kinetics of some specific reactions; and under the heading under this heading, we will talk about enzyme inhibition. Till now we have talked about reaction rates, rate laws, effect of temperature on reaction rate then complex reactions we also talked about theories of reaction rate then we talked about kinetics of some specific reactions; and under this heading we will deal with this enzyme inhibition. We already have talked about enzyme kinetics that is the bio catalysis, where enzyme is the bio catalyst like chemical reactions normal chemical reactions in biochemical system. This enzymes are acting as catalyst.

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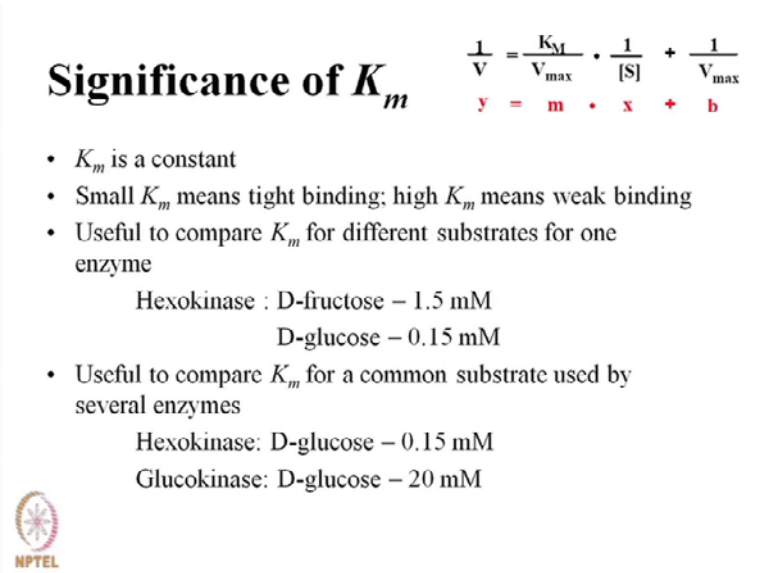

So under this heading enzyme inhibition, we will talk about what is meant by enzyme inhibition and various aspects of this. Now before going into the details of it, let us have some recapitulation now we have dealt with this Michaelis Menten kinetics, where we talked about this K m that is Michalis constant. Now if this Michaelis Menten equation is written in this form there is in this form means 1 by V is equal to K m by V max into 1 by S, where S is substitute concentration plus 1 by V max. So, this is m, this is x and this is c; and this is y. Now K m is a constant. So this is called the Michaelis constant, now small K m means tight binding; there is binding interaction is tighter, so like suppose you have got this is your enzyme; and say this is your substrate, so they are bound tight together. So, it is difficult to separate them up, may be.

So when K m is small, then this is more this interaction is more that is binding is tighter; and high K m means weak binding. So when K m there is Michaelis constant is high, then binding interaction is big. Now this is useful I mean this K m is very useful you know to compare you know this various reactants; and they are you know how efficient, you know some enzyme is with respect to some reactant or with respect to around different reactant. Now so for, for example, if we think of this Hexokinase this enzyme now when the substrate is D fructose it is 1.5 mill molar k m is 1.5 mill molar whereas, for d glucose it is .15 mill molar, so the value of this, I mean this for D glucose is K m value of K m for D glucose is less that means you know here it is tight binding. It is also useful to compare K m for a common substrate used by several enzymes like Hexokinase

and Glucokinase for Hexokinase D glucose case; it is .15 milli molar whereas, for Glucokinase d glucose it is 20 milli molar.

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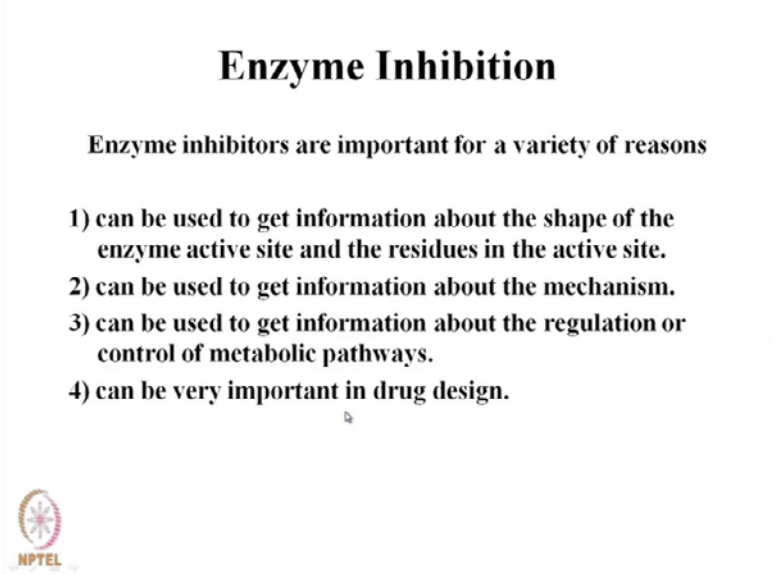

So value this value is higher compared to this value. So, we can we can compare you know compare whether the binding is stronger or the binding is weaker. Now enzyme inhibition, now enzyme inhibitors are important for a variety of reasons. Now it can be used to get information about the shape of the enzyme active site you know you have got suppose you have got enzyme

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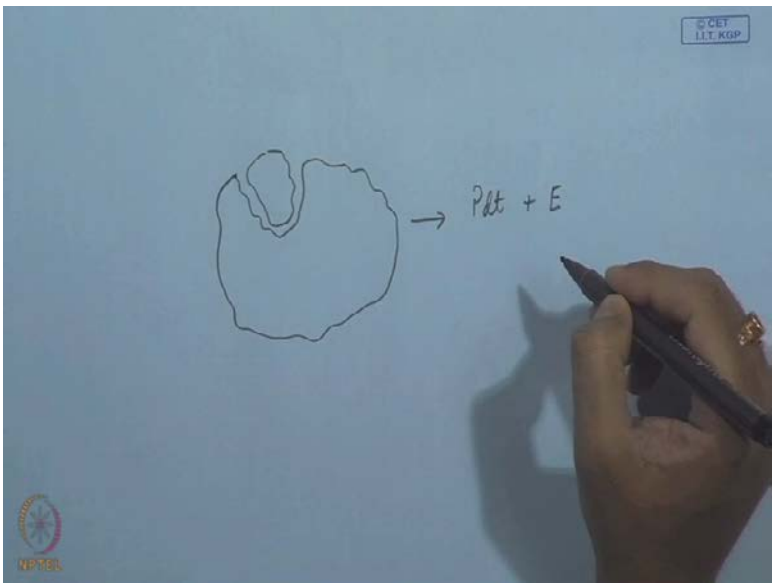

like this, it is basically a protein; and say this is your active site .So this active site in this active site suppose you are your reactant fits, and then chemical reaction takes place and after that your product is formed plus your enzyme is returned back. So inhibitors are used you know to find information about the shape of the enzyme active site. This site may be, and the residues in the active size. So there are residues in these active sites.

So may be in this region in this in this region this active site, so residues are there, so which residues are there and which residues are important compared to the other that we can that we can get information about, then then it can be used to get information about the mechanism, so to get the information of the mechanism or how this reaction is taking place.

So mechanistic part is also you know we can we can find out the information of that. It can be used to get information about the regulation or control of metabolic path ways. So using in in using various inhibitors, we can find out this things; and also for drug design. These studies are very important that is enzyme inhibition studies are very important.

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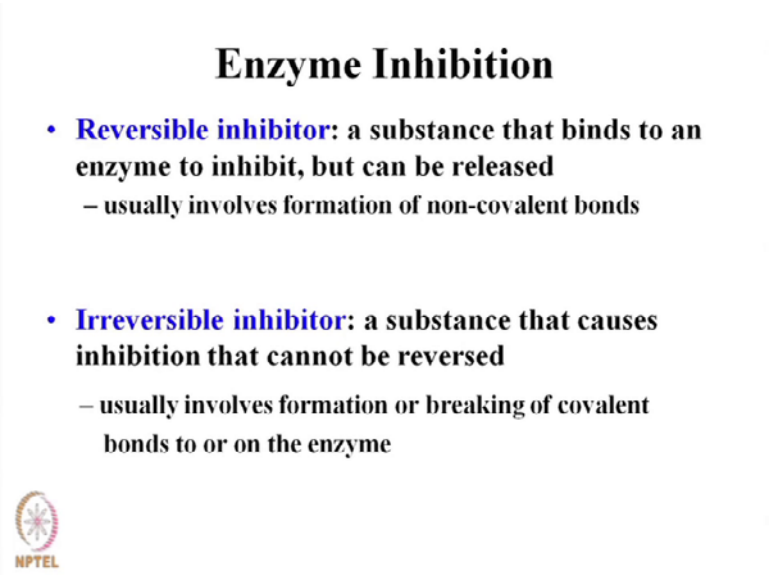

Next types of inhibition, one is called you know you know when when it is the question of inhibition that means we need an inhibitor. So reversible inhibitor is basically a substance that binds to an enzyme to inhibit the reaction but, can be released in a reversible fashion see usually involves formation of non covalent bonds may be some

vander waals interaction may be hydrophobic interaction or may be some electrostatic interaction.

So these are the three non covalent mode of modes of interaction by which this inhibitor can bind with with enzyme. Next is irreversible inhibitor what is an irreversible inhibitor? It is a substance that causes inhibition that cannot be reverse. So it is a it is a reversible formation of bond that is usually it involves the formation or breaking of covalent bonds that is breaking up covalent bonds may be within enzyme or may be formation of new bonds that is a it is basically a chemical transformation of your enzyme.

So therefore, the enzyme loses its activity, and in a it is an in I mean irreversible fashion but, for reversible case since the binding is not a covalent interaction I mean bond is not a covalent bond so may be may be it can be reverse back. So because, because like a hydrophobic hydrogen bonding may be electrostatic or van der waals interaction. These are the modes of interaction for reversible inhibition.

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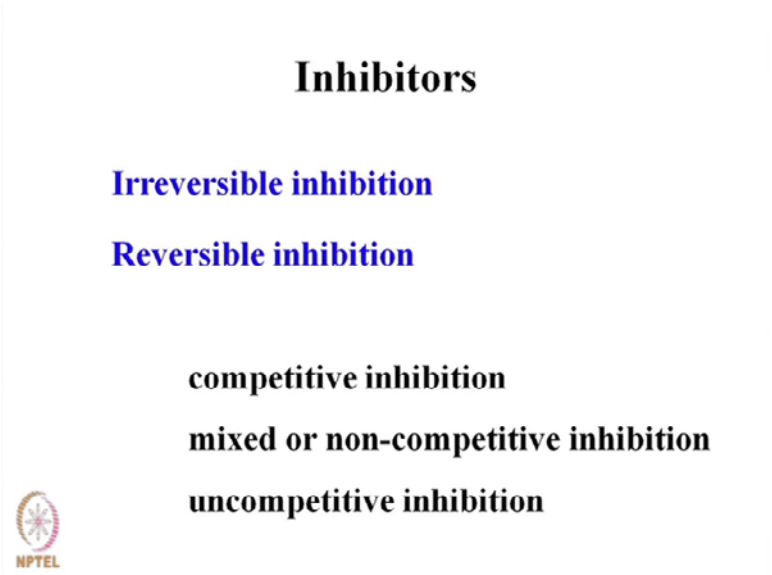

Now so when we talk about irreversible or reversible you know inhibition you know there there are other things that we should take into account, one is you know there are there are three types of broad classification with respect to inhibition, one is competitive inhibition, next is mixed or non competitive inhibition, third is uncompetitive inhibition.

So competitive inhibition mixed or non competitive inhibition and the third one is uncompetitive inhibition, so competitive, non competitive, uncompetitive.

So these are the three types of you know inhibitors. So maybe you can you can call like competitive inhibitor may be in another case you can call non competitive inhibitor or the way uncompetitive inhibitor.

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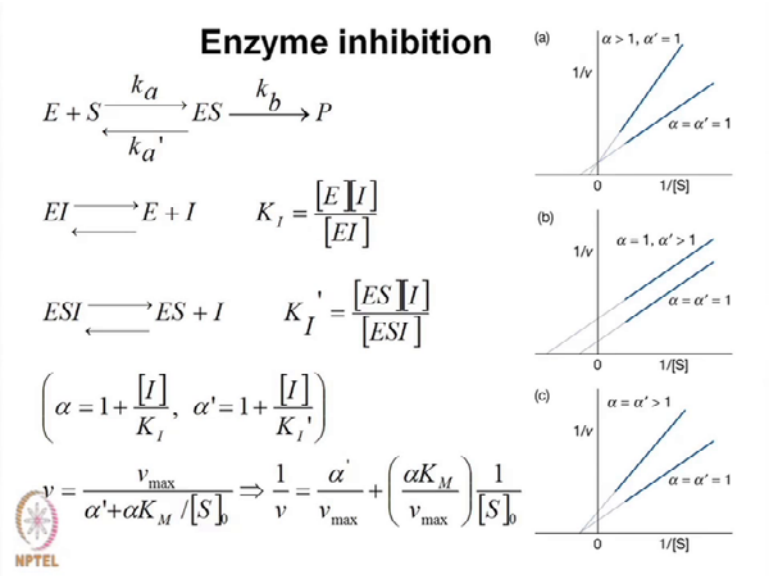

So let us look into the the chemical scheme for enzyme inhibition. See, in this particular stage scheme enzyme plus substrate producing enzyme substrate complex, then it produces the outcome outcome that is your product with a say rate constant of k b, this is associate I mean k is forward rate constant for ES formation and this is the backward rate constant, I mean the disassociation of ES complex. The movement you add some inhibitor what is going to happen? that may be this inhibitor directly minds to the enzyme producing enzyme inhibitor complex like this EI giving rise to E plus I back to EI, so this is one one reaction.

So this is K i and this is for your I mean inhibitor disassociation process or may be or or may be the reverse processes enzyme inhibitor complex formation, and the followed process is enzyme inhibitor disassociation. You can think in in other way also I mean you can write this reaction in a in a reverse fashion. Another situation is enzyme substrate, then it minds to inhibitor producing enzyme substitute inhibitor then it it gives you know in a reversible fashion enzyme substitute plus inhibitor. So the corresponding

equilibrium constant can be written as this. We are defining one quantity alpha which is 1 plus i by K i or alpha prime is 1 plus i by K i prime, and in this case v can be written you know in this fashion and if we plot plot in this way 1 by v verses 1 by S, then we see that there are three situations when alpha is greater than 1 and alpha prime is equal to 1 this 1 we are we are getting alpha is equal to alpha prime is equal to 1 this is another situation.

The second situation is alpha is equal to 1 alpha prime is greater than 1 I mean this this this the second means this one in in second you know for the card b and here you see that alpha it is equal to alpha prime is equal to 1. So this may be another situation, third situation is that like this and you see that difference is that you see that for this 1 the intercept same for both cards you see that this two intercepts are different and also it is cutting the 1 by by S axis at different points here also they are cutting at different points here we see that this intercepts are different but, they are cutting at the same 1 by S axis, so how this is coming? we we will be discussing later on.

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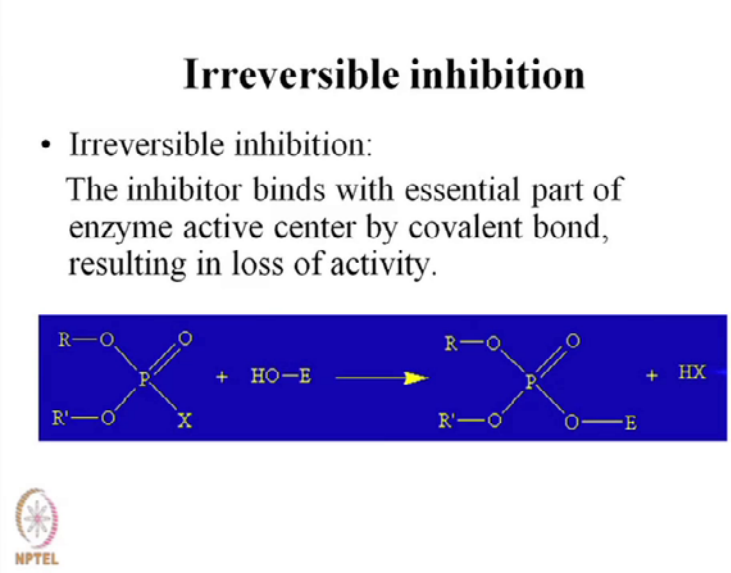

So these three situations may be may be may be may be considered. Irreversible inhibition the inhibitor binds with the essential part of the enzyme active center by covalent bond resulting in loss of activity for example, say this schematically written in this way that say this is 1 reactant this is your enzyme E. So it is producing something like this and HX something else also another another you know resulting substances

produce but, you see this this is a covalent bond formation, so that means enzyme activity since this is a permanent bond formation, so enzyme is no longer enzyme is in no longer free, enzyme is no longer free to react with another substrate. So the reaction after after this reaction happens no further reaction is taking place, so that means the enzyme losses its its activity. So this is called a irreversible inhibition it is not a not in a reversible fashion so backward reaction is impossible or even if it happens it happens to an infinitesimally small extent, so that that is practically not you know of any significance.

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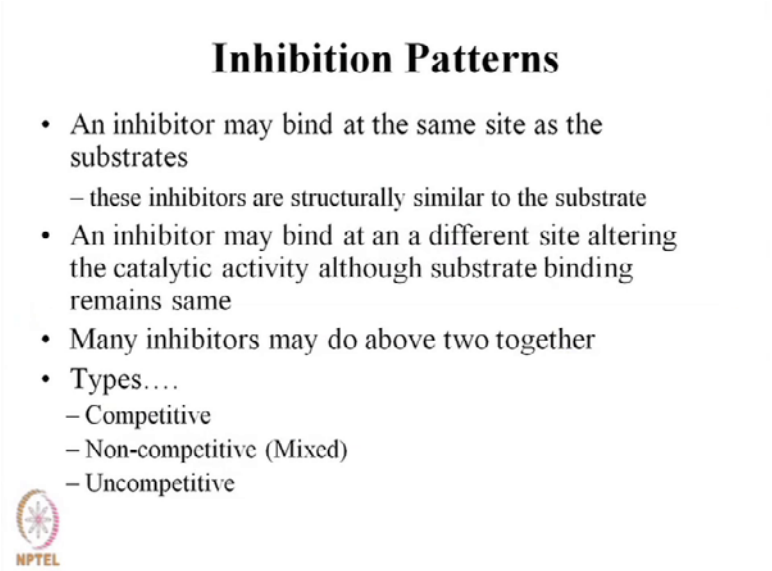

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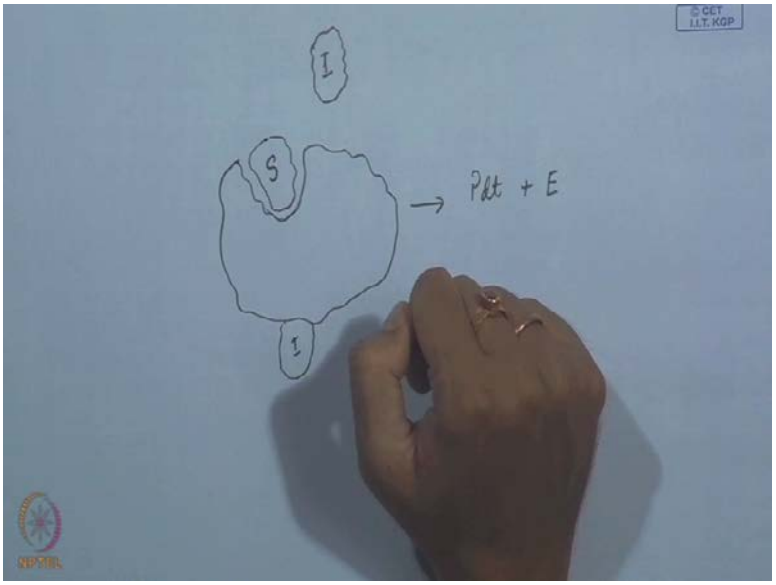

So this is basically a schematic representation of irreversible inhibition. Now inhibition pattern an inhibitor may bind at the same site as substrates that means suppose you have got this enzyme say this is your your substrate and say this is another similar looking inhibitor. They have got resemblance in their structure so may be what is happening that it will come over here that is it will compete with this, so this one also this one these two are having the probability of binding to this or occupying this this space.

So so they are structurally similar so they are having structural resemblance and as a result of which they will bind to the same active site. Next situation is an inhibitor may bind at different site, and there by altering the catalytic activity although substrate binding remains identical. So suppose your enzyme is this and your inhibitor binds at some other place in such a way that suppose here it binds your inhibitor, and it modifies your active site or active site activity in an indirect fashion, so that reaction gets slowed down. Although apparently this particular site there is active site is not distant but, because of this binding some internal structural change may happen as a result of which this enzyme activity may get reduced. These are third situation is that many inhibitors may do both of these that at the same time it may bind here also bind at a different place. So they are doing in a in a in a in a parallel fashion may be. As I told you that the type of inhibitors I mean inhibition is competitive, non competitive or mixed and the third one is uncompetitive.

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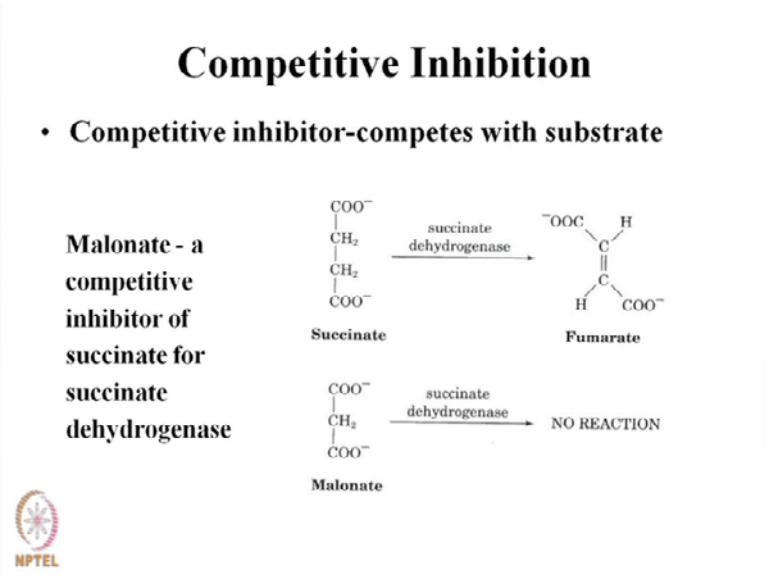

So competitive inhibitor it competes with the substrate suppose suppose you have got similar kind of you know substrate inhibitor then what is happening that enzyme does not know which one which one whether this 1 is is is its right substrate or this one is its right substrate but, two as this is is our right substrate.

So what is happening that it becomes difficult since they are having structural resemblance it is difficult for the enzyme to discriminate between these two, and as a result of which it is said that these two compete for the for the same active site. Malonate is a competitive inhibitor of succinate for succinate dehydrogenase like the scheme shown over here. Although you know succinate for succinate after adding succinate or in presence of succinate dehydrogenase it produces Fumarate but, here no reaction occurs but, there are having some structural resemblance because, it is a you know diacid this is also diacid although it is only one CH 2 spacer there are two CH 2 spacers. So for the formation of a double bonding meet another C. Since it is not available over here so no reaction occurs but, although they are having structural resemblance, so they are competing each I mean competing for the same enzyme there is succinate dehydrogenase.

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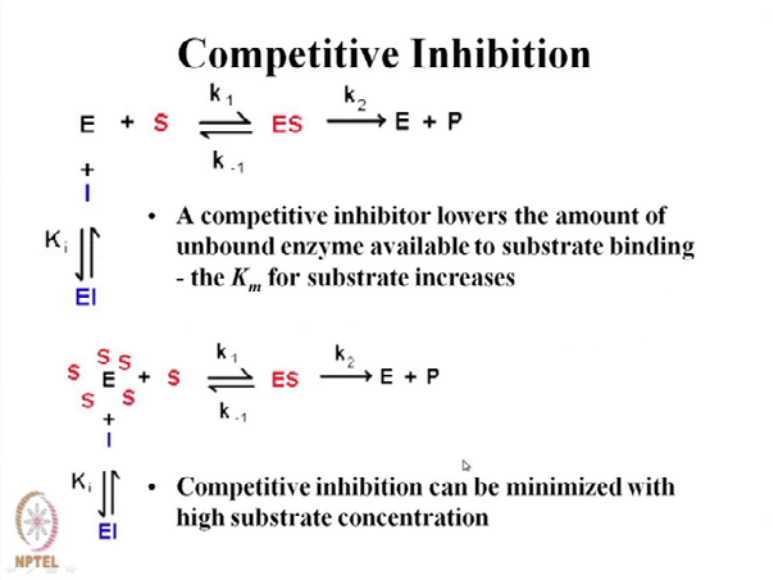

Next competitive inhibition the scheme is like the classical scheme there is the this is the normal scheme enzyme, substrate, enzyme substrate complex, then enzyme back then product. Now since the inhibitor is present there along with your substrate what is

happening? Now this inhibitor again binds with your enzyme, so what will happen? with with a with binding constant K i producing EI.

So a competitive inhibitor lowers the amount of unbound enzyme available to substrate binding and as a result of which K m for substrate increases, K m per substrate increases means you're in you know binding is less as I told at the very beginning, now what will happen? the other situation is that if you add your substrate to a huge extent huge extent means that the substrate concentration is very high, then what will happen? that concentration if we if we take the concentration ratio of substrate to inhibitor then the ratio for substrate to you know substrate is more I mean more amount of substrate is is there. So what is happening that may be almost all the enzyme molecules are you know are surrounded by many substrate molecules compared to I inhibitor.

So what is happening, so probability of binding of the substrate molecule increases since you increase the concentration of your substrate, so that this path is you know more accessible than this path so this is happening parallel but, since the concentration of your substrate is very high is very high therefore, this is the majored channel so competitive inhibition can be can be minimized with high substrate concentration. It cannot be eliminated but, it can be minimized that is the effect can be minimized with high substrate concentration.

So what is happening for your competitive inhibition a competitive inhibitor lowers the amount of unbound enzyme available to substrate binding and they are by K m for substrate increases, and if we increase the concentration of your substrate then competitive inhibition remains but, the effect is minimized the effect is minimized because, more of substrate are there so probability that the substrate will bind enzyme is more as a result of which your normal reaction path is more promoted compared to this inhibition path.

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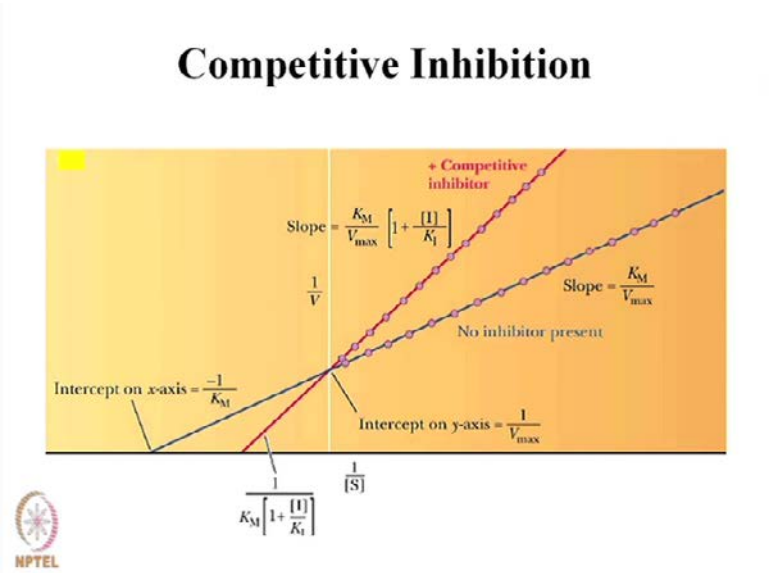

Next so the corresponding a plot 1 by V verses verses 1 by S you see that this is for your no inhibitor present no inhibitor present and this is for your competitive inhibitor present. Let us go back to the earlier slide this one you see here you see that this is 1 by V axis intercept for both red and blue curve same but, corresponding you know meeting point at on the 1 by S axis you see the intercept on x axis it is 1 by K m minus one by K m you see this is nearer to this point and this is farther.

So an intercept is 1 by V max so maximal velocity remains the same, and the slope you see K m by V max so V max 1 by V max same for both, so K m is different so Michelis constant is different so for your competitive inhibition if it is a case of competitive inhibition you will be getting a curve I mean plot like this in absence of inhibitor and in presence of an inhibitor. So this type of plot you may expect for a competitive inhibition as I told you in the in the here also you see so this is a case of this is a case of competitive inhibition so three possibilities are there, so first possibility we are just a we have just explored.

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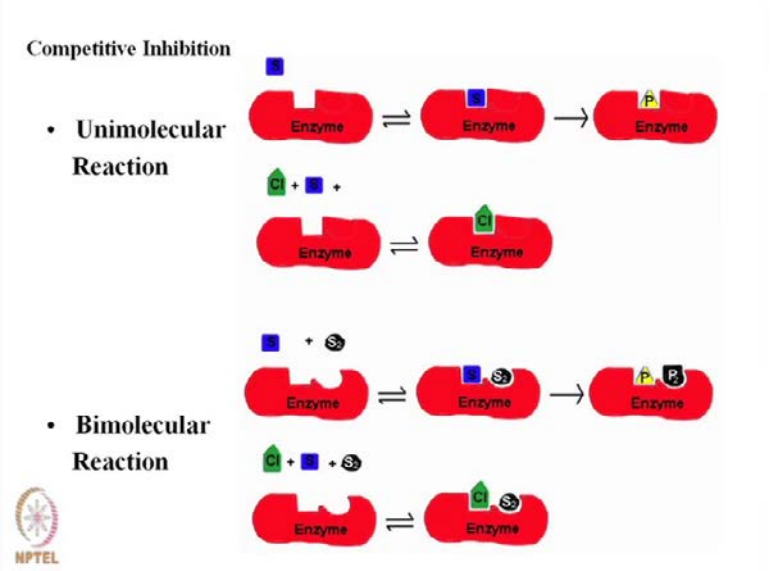

So pictorially competitive inhibition for a unimolecular unimolecular reaction enzyme substrate enzyme substrate complex then product then product will be reduced and enzyme will be freed to come back to here and do the do this in a cyclic fashion, so in presence of a competitive inhibitor what is happening that your enzyme is here they look very similar you see this part and this part they will do very similar although this side is different it is pictorially you know demonstrating this way you see that this one is having the option to bind here you know take this place or may be this one can attach over here. So what is happening that if it attaches then substrate cannot access this this pocket for the reaction to take place.

So basically enzyme competitive inhibitor complex now what what you can do is you can increase the concentration of this substrate, so probability wise if if it is very high, then competitive inhibitor cannot compete concentration wise and as a result of which more of substrate will bind to enzyme to give give rise to products so there by you can minimize, so it is a unimolecular case that one pocket one substance, now if it is a case of two pocket and two substance then you see this is your substrate and this is another substrate, so you see that substrate one substrate two it is producing enzyme substrate complex then giving rise to products.

Now if you have if you have you're a competitive inhibitor over here so which will compete with this S, then in place of S this competing inhibitor will take this this place,

so that to have this further reaction you know since inhibitor is here so for that reaction basically cannot take place. These these are basically pictorial representation so the pictorial representations of the enzyme pocket.

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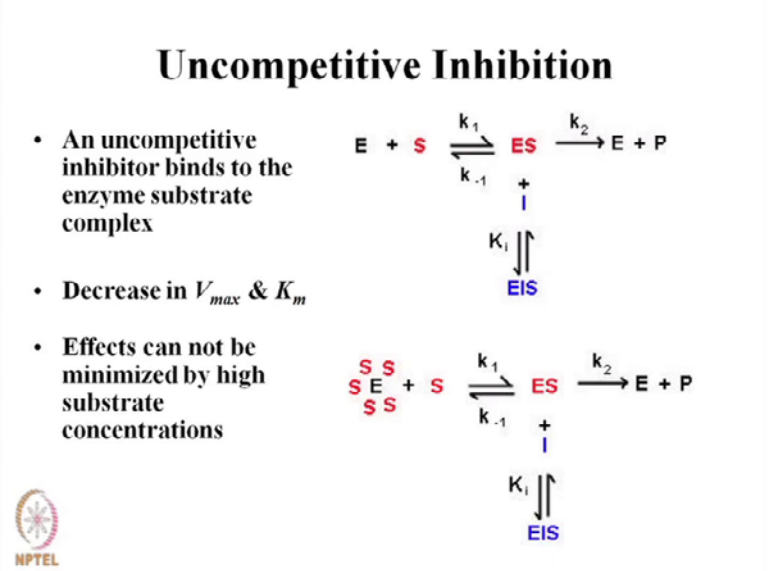

Next is uncompetitive inhibition what is the uncompetitive inhibition? that your uncompetitive inhibitor binds to the enzyme substrate complex. It it does not bind to your enzyme, so what happens is that once enzyme substrate complex is formed, then this has got two options either it will go it it will go this way to produce a product or it will move this way to give rise to enzyme inhibitor substrate complex or sometimes it is called as ESI or EIS, so what happens the decrease in V max and K m, now you see if you increase the substrate concentration suppose there was one S initially now increase it to 6 1 2 3 4 5 6 so it will happen that if you increase this substrate concentration more of ES will be formed and the more this is formed that is enzyme substrate complex is formed it has got more option to more option to move to this pathway.

So that means you you cannot minimize this state because, you know you can you can stop this process because, this process is very much dependent on the availability of ES so therefore, this effect of this uncompetitive inhibition cannot be cannot be minimized cannot be minimized with cannot be minimized with high substrate concentration. So if you go back to competitive inhibition you see that here the inhibitor binds directly with enzyme directly with enzyme but, in case of uncompetitive it does in a different fashion

that it binds with enzyme substrate to produce enzyme substrate inhibitor a different complex and once it is formed it cannot give rise to this this that is your product and there is a change in V max as well as K m,

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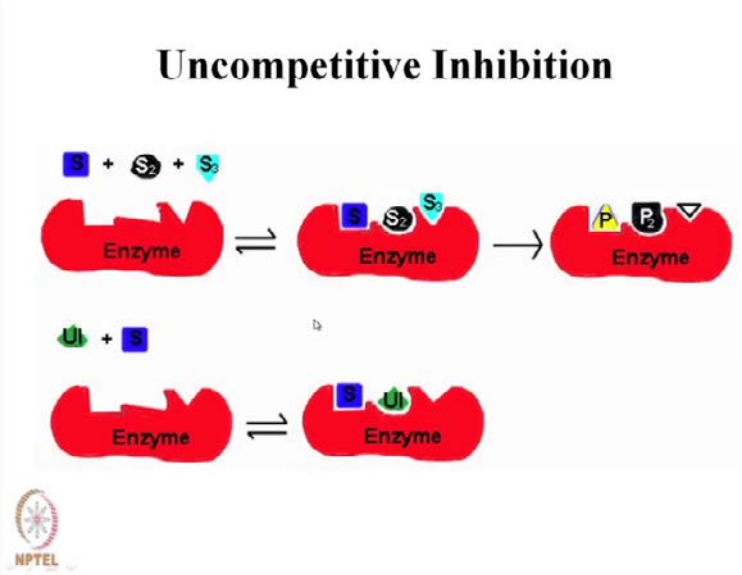

so uncompetitive inhibition you see substrate this is another substrate this is the you know third substrate, so what is happening these three are you know binding with enzyme to produce to give rise to product P this is a product then P 2 and and also, something over here. So in presence of uncompetitive inhibitor say substrate binds giving us the enzyme substrate and then uncompetitive inhibitor binds over here once it binds then this S 2 cannot access this site.

So reaction stops over here you see that this uncompetitive inhibitor inhibitor binds with enzyme substrate complex not with the free enzyme its action is important when substrate is bound already bounded the enzyme with the enzyme, so when substrate is not present its action is you know it is not designable you cannot cannot see its action but, the movement substrate is present in binds it stops the enzyme activity it stops the enzyme activity

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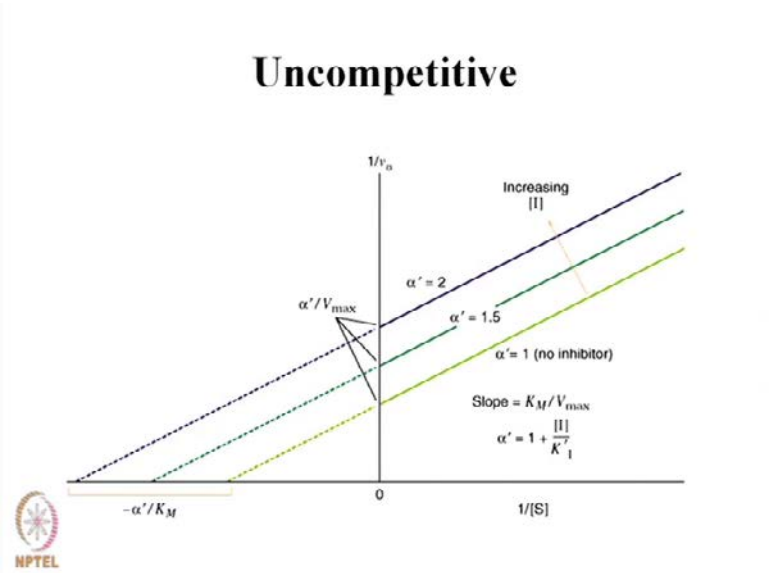

This is uncompetitive you see for uncompetitive this inhibitor increases, and the corresponding plots you see that this this numbers this this intercept on a y axis it is you know changing and also this intercept is changing, so both V and also V max and also Michaelis constant these are changing for an uncompetitive situation, so for your competitive you see it is one point on your y axis and two different points on your x axis you see here three different points on y three different points on x axis of course, in negative fashion so this is uncompetitive situation.

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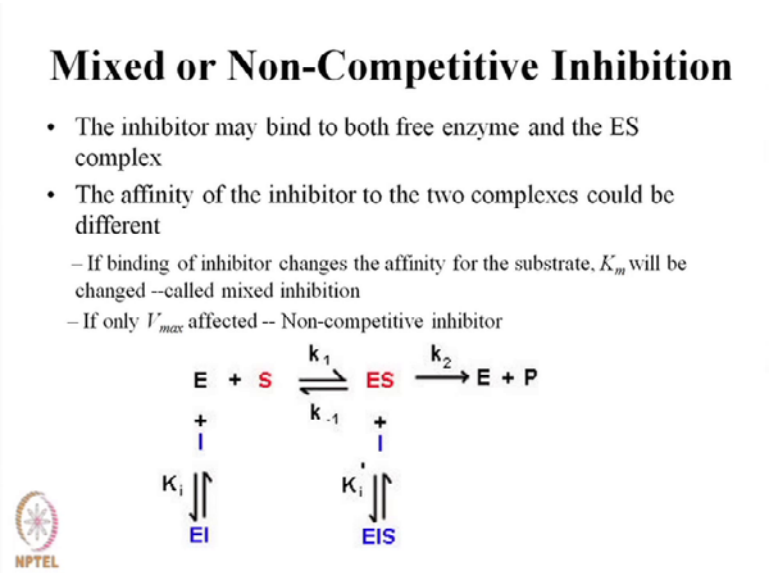

Next next or non competitive inhibition now the situation is the inhibitor may bind to both free enzyme as also the enzyme substrate complex. The affinity of the inhibitor to the two complexes could be different if binding of inhibitor results in a change of affinity for the substrate K m will be changed and as a result I know and the the name is mixed inhibition, if K m is changed but, if only V max affected then it is called non competitive inhibition.

So two situations mixed inhibition K m will be changed non competitive inhibition V max will be affected, the scheme is kinetic scheme is this enzyme substrate producing enzyme substrate complex giving rise to your enzyme back and product now this enzyme can bind to both I mean this ES as also E with K i for E and K i prime for ES so giving rise to EI for here, and enzyme inhibitor substrate complex for here but, remember for your uncompetitive situation is like EIS,

so only the enzyme binds over here with enzyme substrate but, not with your enzyme but, here non competitive or mixed fashion you see that enzyme binds with ES and I mean your inhibitor binds with ES and E with different you know rate constants I mean equilibrium constants EIS and EI so if K m is changed is called mixed if only V max is affected it is called non competitive inhibitor.

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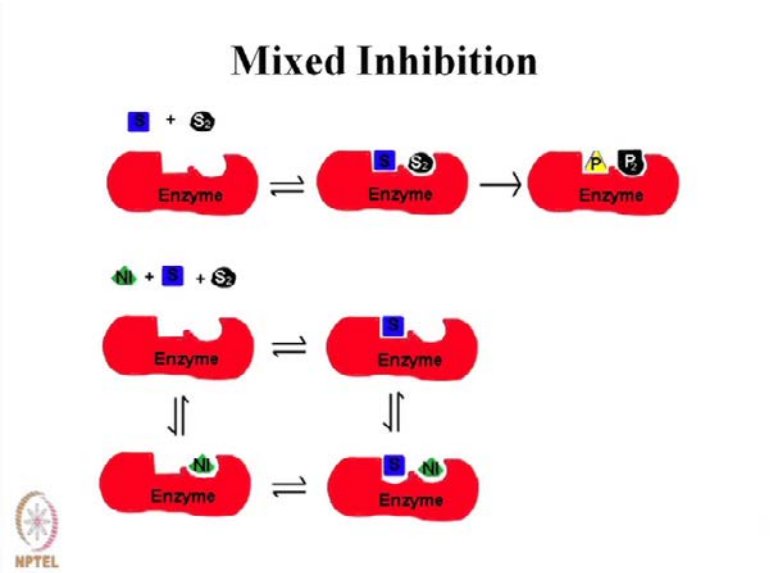

You see mixed inhibition substrate enzyme this is another substrate, so it is basically a bimolecular scheme, so substrate binds with enzyme producing enzyme substrate another

S 2 also binds over here giving rise to your product you see this is a case of mixed inhibition I mean non competitive or mixed inhibition you see non competitive inhibitor substrate substrate 2 first substrate binds then in presence of non competitive inhibitor this is produced or in another situation your enzyme first noncompetitive inhibitor binds then in presence of your substrate it gives rise to this, so basically this enzyme free enzyme and enzyme substrate inhibitor they are in equilibrium higher these two may be intermediates.

So these four are in equilibrium so that is why basically you can you can put you know basically enzyme inhibitor then enzyme inhibitor substrate just put one substrate over here so that these four are in equilibrium, and only enzyme substrates channel can give give rise to this enzyme plus product so probability wise enzymes are free enzymes substitutes is reduced and reaction rate is lowered.

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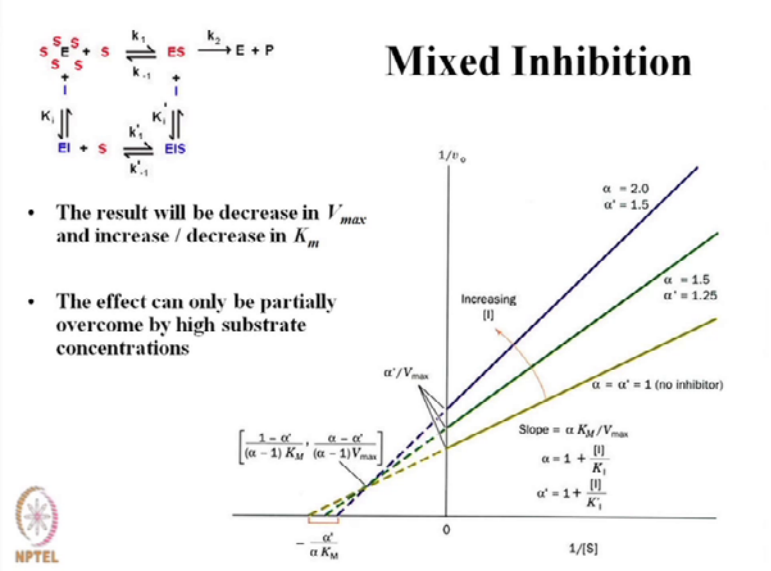

So it is called the mixed inhibition. So so this is the scheme enzyme substrate enzyme substrate then giving rise to I means enzyme plus substrate giving rise to enzyme substrate then product plus enzyme in presence of inhibitor what is happening? enzyme inhibitor substrate then this is an equilibrium with enzyme inhibitor then enzyme inhibitor is equilibrium with this one.

So this is the this is this is the equilibrium scheme you see as I have shown over here this is the equilibrium they are these four species are in equilibrium now what is happening

that if you put so you see here there is one channel through which you can get your product. So if you increase your substrate concentration to huge value huge number then what is happening? That possibility of this step I mean this channel is a little increased although these steps are there.

So you can partially overcome the effect of this inhibition mixed inhibition by increasing your substrate concentration so what is happening as a result of which what is happening you see that V max is decreased and K m may get increased or may get decreased you see these are three situations you see this is increased inhibitor is increased you see and this cutting point is here in between not on your on y axis.

So three distinct situations are there this is your mixed or you know non competitive come back to earlier slide that this is one case, this is the third case, this is the second case uncompetitive this is the non competitive or mixed inhibition, so for your mixed inhibition like your competitive inhibition is a kind of competitive kind of but, not exactly a competitive it is a although it is a non competitive but, it has resemblance to your to to competitive that you can partially overcome although competitive inhibition can be greatly overcome with high substrate concentration here also you can you can cannot fully overcome but, you can partly overcome with high substrate concentration.

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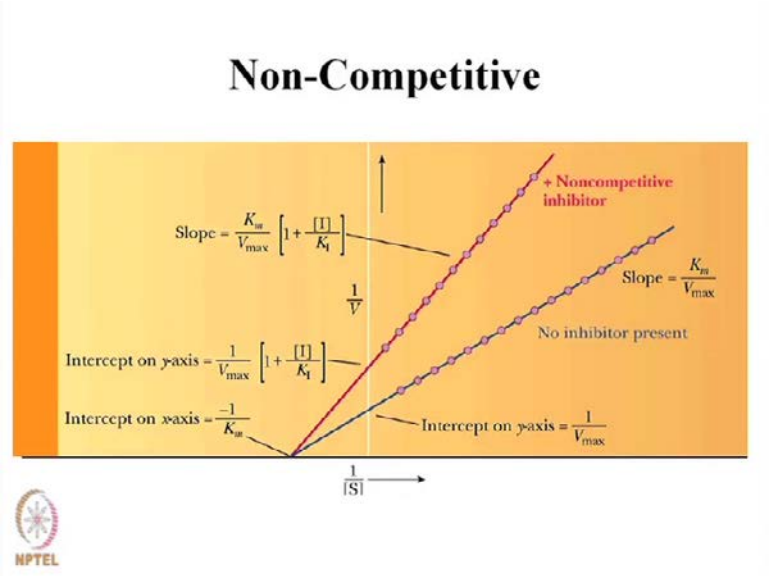

So this is a typical plot for your mixed inhibition. So general a non competitive inhibition you see no inhibitor present this one non competitive inhibitor you see it is

here K m is remaining same k m is remaining same so K m is remaining same means you see this is a non competitive inhibition, if K m is affected it is called mixed inhibition you see here K m is affected k m is affected.

So here K m is not affected so it is called your non competitive inhibition, so if this cutting point is somewhere over here then K m will be affected but, if if this cutting point is here then you know K m is not affected you see only V max is affected you see 1 by V max over here there is another one I mean the the different 1 by V max, so V max is affected.

So that is why it is a non competitive inhibitor again go back to competitive inhibition you see the typical plot for competitive inhibition this one you see K m is changing but, V max is remaining same and a non competitive K m is fixed V max is changed and the this is because, your scheme has changed scheme means the reaction scheme has changed and as a result of which your you know the plot is different.

So let us go back to this slide, this is your non competitive inhibition this is your competitive inhibition this is uncompetitive inhibition so basically we can we can explain these three you know crabs arising out of a you know you know using using enzyme kinetics when when we talk about enzyme inhibitors and three types of three broad classifications are there competitive, uncompetitive and non competitive that is competitive, uncompetitive and non competitive.

So for your competitive inhibition V max is not changed only K m as I told you K m is you know K m is increased and K m is increased means you're you know binding is less binding affinity is less less as a result of the presence of your inhibitor, for your uncompetitive it is a different situation that you get two parallel plots as if these two are you know occurring in an unconnected fashion as the third one is has got connection over here you see that K m is not changed but, V max V max is changing.

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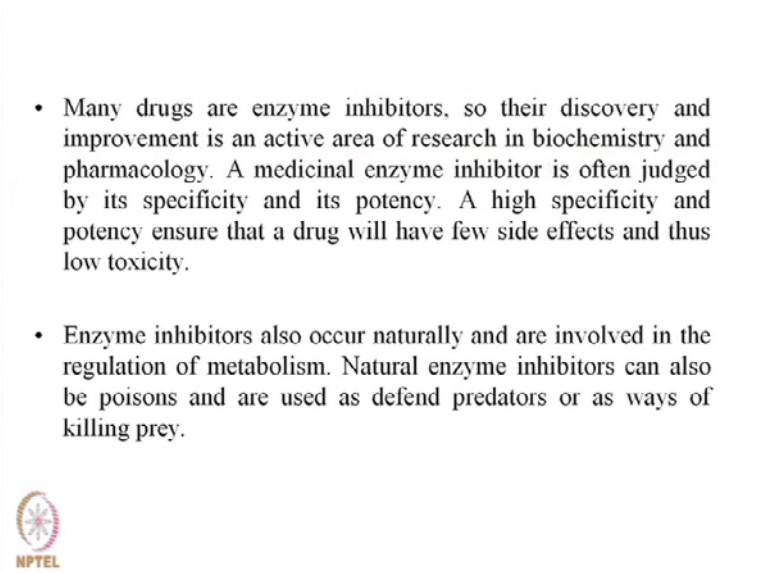

So now why have we a have we learnt this enzyme inhibitors what is the necessity of a exploring this one? now many drugs are enzyme inhibitors enzyme inhibitors means sometimes you need to inhibit the action of some of the enzymes within our body for some you know for some reason or in some cases suppose in presence of some inhibitor some physiological you know process are impaired.

So in that case you need to remove your inhibitor. Now many drugs are enzyme inhibitors, so their discovery and improvement is an active area of research in biochemistry and also in pharmacology. A medicinal enzyme inhibitor is often judged by its specificity and its potency. Now by it's a specificity and potency means specificity means how specific its action is and a high specificity and potency ensured that a drug will have few side effects and thus it will have low toxicity. Toxicity means side effects suppose we are putting a drug we are giving a drug which has got side effects means it is parallely affecting other a biochemical channels. It is affecting our our interest I mean our our I mean the channel which we are interested in along with other channels which which is not a desirable.

So we need to you know we need to minimize the side effect and you need to minimize the toxicity, so that's why high specificity and a potency is very important. Now enzyme inhibitors also occurred naturally and are involved in regulation of metabolism and natural enzyme inhibitors can also be poisons and are used as used to defend a predators

or or as ways of killing prey therefore, natural enzymes are also you know very important and that is natural enzyme inhibitors are also very important .

So summing up what we have learnt let us again come back from come back to starting point that we started with with this Michaelis Menten kinetics. We talked about the significance of K m already we have a discussion in in in a in an earlier classes about this Michaelis Menten kinetics. Now the significance of smallness or largeness of K m is discussed with the help of you know line we were bar plot we tried to explain various types of you know inhibition effects.

Now you know enzyme inhibitors they are why why they are important because, which in a you know information's are necessary I mean that I mean basically you want to get information about there is I mean active sites and also the residues that are important in the active sites we want to get information or we want to get idea about the mechanism that is why studies on on inhibition is very important how metabolic pathways can be affected? With the help of inhibitors.

we can study that and also most importantly drawn design because certain drugs are enzyme inhibitors that means if we put that drug or we if we administer the drug then it will bind to the active site of the enzyme or it will it will trying to change you know the the local site of your active region of the enzyme by some secondary effect may be it is binding to a distance point from the active site and it changes the activity.

So the study of this enzyme inhibition is very important. Types of inhibition whether it is reversible or irreversible talked about it reversible inhibition means it is a non covalent bond formation and irreversible inhibition means it is basically a formation of a formation of a covalent bonds or rearrangement of number of covalent bonds within the enzyme or may be in in the enzyme substrate or enzyme inhibitor complex, now a now a competitive inhibition, non competitive inhibition and uncompetitive inhibition.

we have talked about then the basic kinetic scheme we have given and three different situations can be can be obtained out of it one is for competitive another is for uncompetitive and third one is for non competitive inhibition we have given the idea of irreversible inhibition that is irreversible irreversibly this enzyme is transformed to something else.

Now different inhibition patterns we talked about we talked about your in details taking each situations like for your competitive inhibition how it is operative? How this can be minimized? And the linear if I part plot for your competitive inhibition and its characteristics then with the help of pictorial diagram.

we try to explain the competitive inhibition then we went to competitive I mean uncompetitive inhibition and the corresponding diagram liner we have bar plot then we came to non competitive inhibition and with the help of this diagram I tried to explain the corresponding liner we have bar plot it is the non competitive case how does it look whether we means whether we are getting a different K m or not.

So it looks like that we are getting same K m but, different V max for your non competitive case although for next case its different you see here this different K m and different V max, and the importance of enzyme inhibitors we try to give you some idea why we need to study and actually this inhibitors studies are very important for rational drug design. So this is very important this is very important means the study of enzyme inhibitors is a very important.

So with this words we would like to I would like to conclude this session, so in the next session we will talk about this kinetics of autocatalytic reaction and oscillatory reactions so till then good bye.