Drug Delivery Principles and Engineering
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Lecture – 03
Pro drugs and Polymers Introduction

Hello everyone. Welcome to another lecture of Drug Delivery Principles and Engineering. In the past two lectures, we had discussed about why is drug delivery required and what are the pharmacokinetics of this. In this lecture, we are going to finish the pharmacokinetics part and then from there on we will start talking about more in the research and the innovation sides of how if we can improve drug delivery from what is traditionally been known.

So, all of this that we are discussing in the past two classes and today is on what is currently being known and how is the field of the drug delivery is currently going on. And then we are going to talk about more newer systems and today we are going to discuss some polymeric systems that will kind of help in terms of drug delivery enhancement, making sure the toxic effects are low and things like that.

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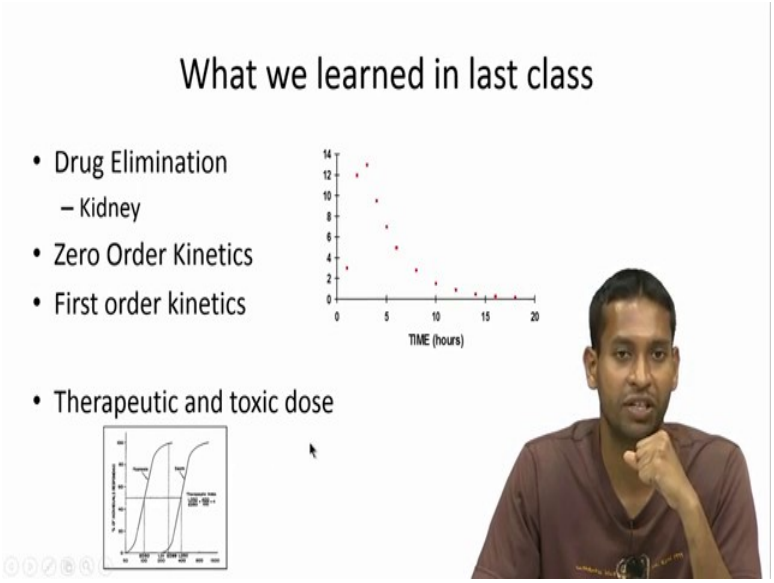

So, before we jump into it, let us quickly recap of what we learned in the last class. So, we first be talking about drug elimination, we talked about how the drug is eliminated

from the body. One the major organ there was kidney and there were other organs involved as well like liver and lungs. But by far the major organ is kidney and what we learned is there is a Bowman's capsule is where this elimination happens, where the drug diffuses out or filters out from the kidney. And typically their filtration limit is about 10 nanometer where if the drug particle is bigger than the ten nanometer, then the kidney cannot clear it out.

Then we talked about different kinetics, so first we talked about zero order kinetics. And, so what zero order kinetics is that rate of elimination of the drug is independent of the concentration of the drug. So, it is constant. So, if the drug is eliminating at 10 ml per hour, it will continue to eliminate 10 ml per hour regardless whether the constant is the drug itself in the blood is 100 ml or 1000 ml; it does not matter.

We talked about first order kinetics which essentially means that the drug is eliminated at a rate which is proportional to the amount of the drug that is present in the plasma. This is most commonly seen with most drugs in the body, and if you talk about pictorially, it is something like this, where you inject the drug it gets absorbed in the body through a certain kinetics and then gets eliminated at the first order. So, you can see the slope here is much higher when the concentration is higher, but as the concentration is decreasing the slope is also decreasing and eventually the slope becomes very low when the concentration the drug is low. And then towards the end of the class we talked about therapeutic and toxic dose. So, essentially talking about what is the concentration at which the drug is therapeutic has a ED50 which is representative effective dose in 50 percent of the population. And then what concentration the drug is not therapeutically active, but in fact becomes toxic to quite a lot of population defined by TD50.

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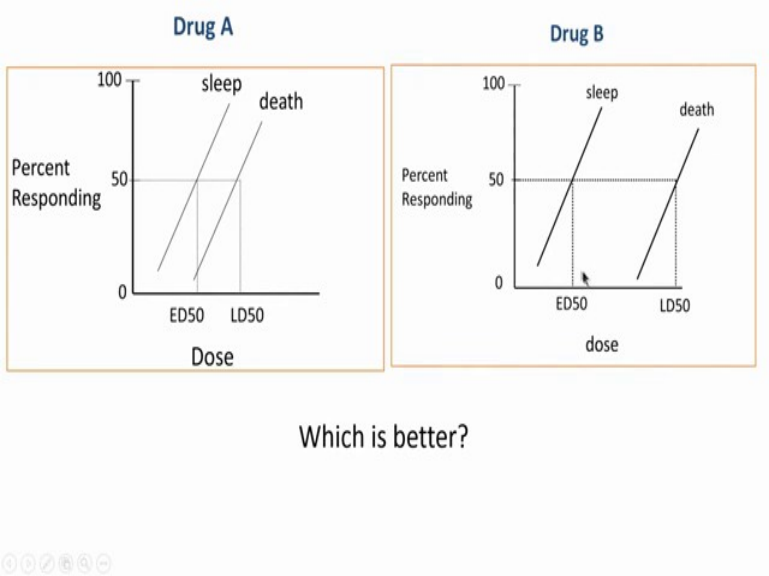

So, let us continue that TD50 and LD50 discussion again, so I have two drugs here drug A and drug B. On the y axis I have percent of people responding to that and on the x axis, I have the ED 50 and LD 50 represented without the labels of the concentration, but on the same scale for the two drugs.

So, can you guess as to which drug is better for the doctors to use? I will give you a moment to decide on that. So, as I am sure most of you would have achieved the correct answer which is the drug B is much better and the reason for that is if you look at the separation between the ED50 and the LD50. The separation is quite higher for the drug B then it is for drug A, because if I want 100 percent of the population to respond to my drug I would have to give a concentration for drug A that will even cause death in some of the patients. Whereas for the drug B that is not the case, I can give very high concentration to drug and that will induce sleep in most of the people, but at that concentration none of the patient will have any kind of side effects.

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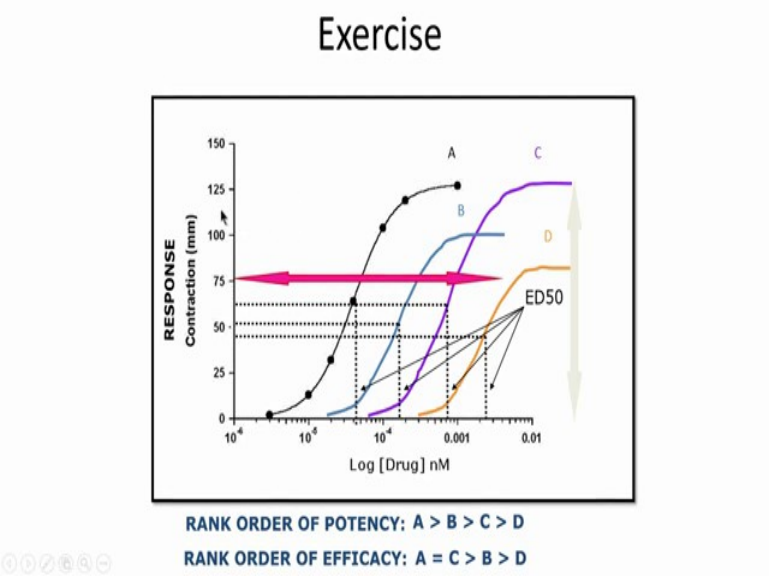

So, another example here is I have now four drugs plotted on the same scale. This again is a semi log scale for the x axis and on the y axis you see the response. So, this is a measure of the response, this is not percent of people responding. This is telling us, how much of a response you are achieving in each of the person. So, you have drug A B C and D and of course, as we know that the ED50 values are also been reported for these.

So, there are two questions that are associated with it. One is can you rank them in order of their potency and then the other is can you rank them in order their efficacy. So, what does the ranking in terms of potency means? It essentially means that how effective the drug is at low concentrations and then the rank of efficacy means that how efficacy. it is versus if it is causing 25 millimeter versus a 50 millimeter contraction.

So, I will again give you a moment to kind of rank these in order of their potency first. So, just let me know that whether B is better than C or A is better than B something like that. So, let us discuss the answer of the rank order of potency first. So, we know that and the ED 50 of the A is the lowest and D is the highest, so; that means, that at a concentration at which A will be effective, all B C and D are not.

So, it is again very simple; that means, that A is the most potent drug followed by B followed by C followed by D in the order of their ED50. What about the rank of efficacy? Again, I will give you a couple of moments to figure that out. So, if we look at

it now, we basically are saying that what is the response these are giving. So, we see that the maximal response that a can give is about 125 millimeter and so does C.

So; that means, that both A and C are giving as similar efficacy to each other, even though A will give that efficacy at a very low concentration compared to C. Remember this is on a log scale. So we are talking about 100 times lower concentration and then C is, but in terms of the efficaciousness both of them give similar maximal response.

So, both A and C are equal followed by B which is next and then D, which is the lowest. So, among all these drugs if I have to prescribe a drug for this application again I do not have the toxicity dose at this point. But assuming the toxic dose for all of them is very high; I will choose A for this application followed by C, followed by B, followed by D unless the toxic dose for C becomes closer than I will have to choose B over C.

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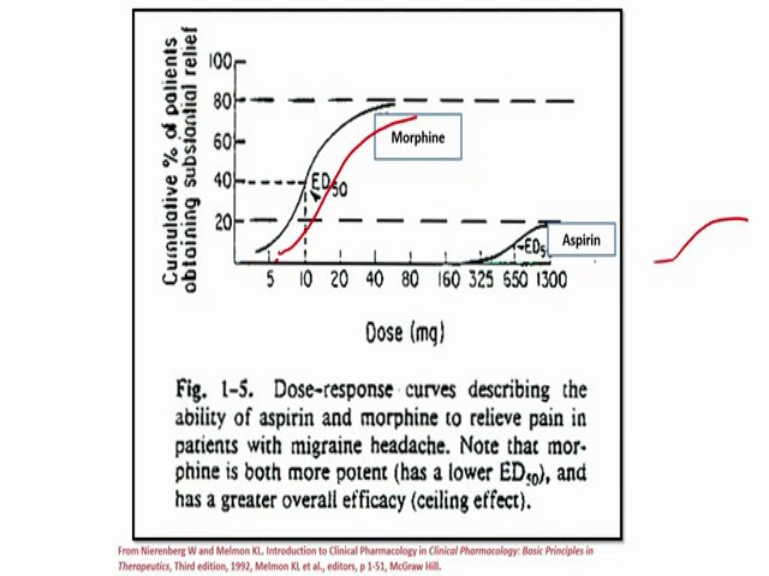

Fig. 1-5. Dose-response curves describing the ability of aspirin and morphine to relieve pain in patients with migraine headache. Note that morphine is both more potent (has a lower ED_{50}), and has a greater overall efficacy (ceiling effect).

From Nierenberg W and Melmon KL. Introduction to Clinical Pharmacology in *Clinical Pharmacology: Basic Principles in Therapeutics*, Third edition, 1992, Melmon KL et al., editors, p 1-51, McGraw Hill.

Here is another example. this is an example which is now widely used. So, you know that both morphine and aspirin have similar applications and that is to get some pain relief. However, we know through literature that aspirin is very widely used compared to morphine even though morphine is much more effective. So, the ED 50 of morphine is only 10 milligram whereas, that for the aspirin is about 650 milligram.

So, morphine is about 65 times more potent then the aspirin, even then morphine is not typically used in people and that is because the toxic effects for the morphine is very

very high, it is very addictive. So, so if I have to draw a toxic curve for morphine, it will somewhat look like this, and that essentially means that even if I give low dose of morphine quite a lot of people will experience toxicity. Whereas, for aspirin it will be somewhere up here which essentially means is fairly safe to give quite a high amount of aspirin.

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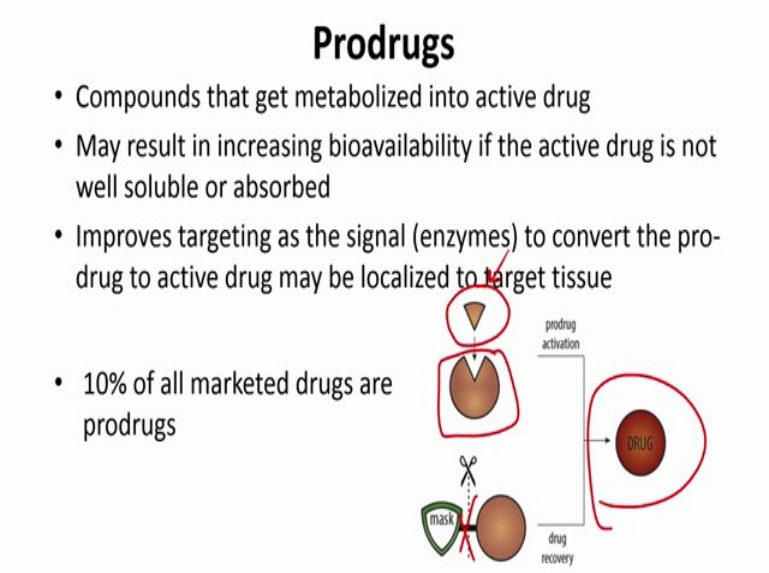

So, next thing we are going to talk about very briefly is prodrugs. These are very widely used in market currently. So, we are going to talk about this first now. And essentially what that means, is instead of giving the drug molecule itself, you use the capability of the body to break down molecules into smaller components as mainly by liver and so you give the components that can metabolize into active drug. And so, why would you want to do that? You would want to do that if you want to increase the bioavailability of the active drug that may not be soluble or there may not be absorbed.

So, let us say if I have a drug which is very very potent, but it is not soluble in water, I cannot give it because if I give it will clog my blood vessels. So, for those types of drugs what I will do is I will essentially make them more bioavailable by conjugating them to let us say a molecule that is very hydrophilic. So, that causes the combination of the molecule and the drug to become solubilized in water and then when it reaches its target organ or when it reaches in the body and circulation it can get metabolized and the active drug can be released.

So, you can even consider this that this is my drug of interest and this is just a tag that I am putting in to cause some beneficial effects. In this case, there is a mask and in this case there is another component that is required from the body itself to essentially give an active drug.

So, as long as this mask is present the drug is not active, but when the mask is cleaved the drug becomes active and the mask is; obviously, removed and excreted through various mechanisms. So, what are the applications area that improves the targeting as let us say I want to target a drug through a certain organ that produces a certain enzyme.

So, I can have these masks or these cofactors such that they are only found in that target organ. So that means, even though my drug is going to go do all different organs only at the organ where it is going to find the enzyme or this cofactor well the drug be active. So, what that helps me to do is essentially minimize the toxic effects, because let us say if a drug that I am using for chemotherapy has toxic effects on cardiac cells in the heart. But then I want the drug to be more in tumor I can give a drug which will break down a mask in the tumor regions, but in the heart there is no such enzyme and so, the drug will have reduced toxicity in the tumor.

Nearly 10 percent of all the marketed drugs at this point of time are prodrugs, so they are very widely used and it is a very effective engineering strategy that has translated into the clinic. And we are going to talk about more and more engineering strategies and like this and different from this that will eventually help you to design and engineer drugs and drug delivery systems, so that ultimate goal is to improve the patient life ok.

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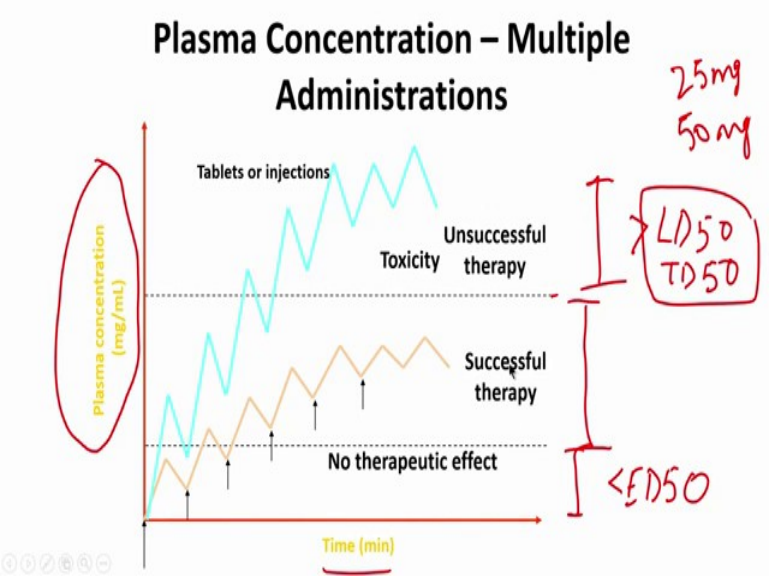

So, this is all basically we talked about in terms of pharmacokinetics, and today we are going to talk more about some more fancier engineered systems. So, just to give you a brief background on this, so let us say on y axis if I plot plasma concentration in mg per ml with the x axis of time. And I am talking about traditional drug delivery where every 12 hours or every 24 hours I am taking a tablet or I am getting an injection and I am trying to figure out what is the drug concentration that I am getting into the body.

So, of course, for any drug as we already discussed there is a LD50 and ED50, so, this region here is something that is essentially below ED50 right which essentially means that if you administer a drug at this point. Nearly all the people that you are administering it to will not show any kind of therapeutic effects.

Anything above this we are essentially talking about being greater than LD50 or TD50. That means, that if I give a drug which is at a higher concentration then this concentration at LD50 or TD50 then there will be lots of toxic effects and that is of course, a complete no in clinics. So, I always wanted to be in this regime, but it is very difficult to be in this regime.

Patients come in with different sizes, patient comes in with different metabolism rate, a kid may only be weighing about 10 kilogram or 20 kilograms whereas, a healthy adult might be 60, 70, 80 kg. So, the drug concentration the doctors need to give is going to be

very different for the two and that is why it is very important for the doctors to know what essentially is required in terms of the concentration.

How easy it is to change this is let us say there are 2 variant drug in the market one is 25 milligram tablet and another is 50 milligram tablet. And if a person is being given 25 milligram tablet let us say time t equal to 0 it builds up a certain plasma concentration of course, it is also gets eliminated here it is shown my straight line, but can be any of the kinetics like the zero order or the second order. Then after 12 hours you take another tablet the so, the concentration builds up even more and this cycle continues. And essentially you get the drug in this regime which is a successful therapy for a longer duration, so the patient gets cured.

However, if you are given a 50 milligram tablet for the same patient what you can have is a profile like this where you get more drugs. So, your concentration arising and essentially what is happening is you have a very limited time in the successful therapy window whereas, most of the time you are in this regime which is toxic.

So, that is of course, not very desirable. The patients will have all kinds of consequences and they will never be cured. So, the whole idea now is to essentially maximize the time in the successful therapy while reducing the drug dose that you are giving to minimize the toxicity and of course, to be high enough to not have sub therapeutic effects.

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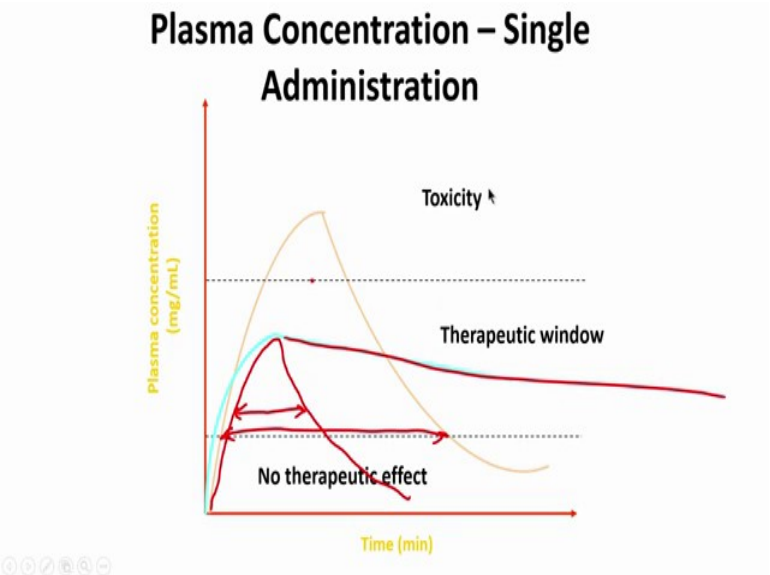

So, now if I zoom into this individual kinetics here, currently what the doctors are doing is they are giving you a dose which is very close to the toxicity level. And the reason they are doing this is because then this maximizes the time for the therapeutic window. If the doctors do not give you that high level and give you a small level, currently what will happen is you will get a regime like this where your time in the therapeutic window is much lower.

So, the doctors currently have to give a dose which is closer to therapeutic levels. So, that it remains in the body for long durations in the therapeutic window for you to get benefits. But essentially what we would like to see is this blue curve where you want the drug once it is administered to be present for long durations in the body in the therapeutic window as long as it is required for the patient to get cured. And so, basically for the rest of the course our target will be to maximize this time in therapeutic window while preventing no therapeutic and toxicity levels.

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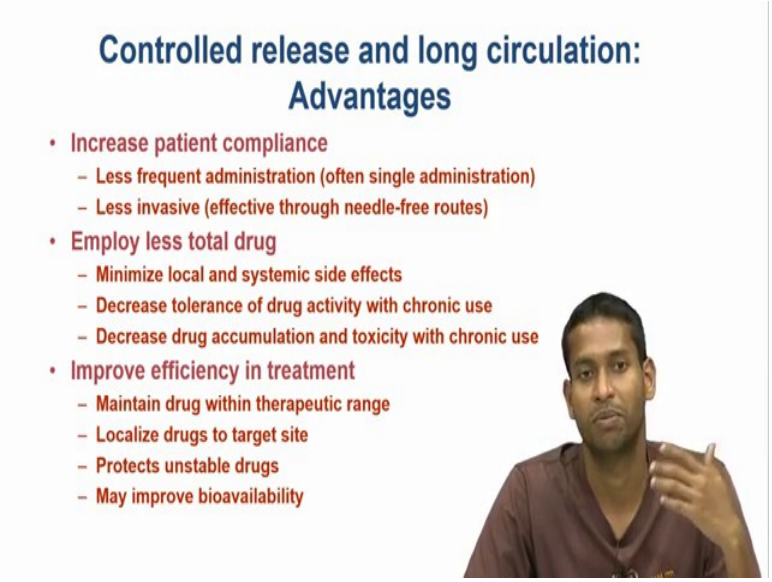

So, that is where the control release and long circulation systems come in and what are some of the advantages that such a system may give why do we want that to be in that regime of successful therapy. It is because first of all it will increase patient compliance why I say that because if a single dose of tablet is going to give you a residence time of 5 days then you do not really want to take 10 tablets for 5 days, 12 hours a day to basically do that. It is it is obviously, will become more patient compliant, patient would rather

take 1 tablet and then be done with it. And especially if it is injections we are talking about then, it is even more patient compliant to just get 1 injection rather than 100s of injections.

It is going to be less invasive, so if we can design systems that are less invasive, so, maybe needle free routes as we will discuss for further in the course those are even beneficial. You will imply total less drug, I mean now we are talking about the drug which is always in the therapeutic windows we are not going to a very high concentration a toxicity level. So, we are administering low amount of drug which is residing for longer, so it will reduce the cost as well as minimize the local and systemic side effects.

And then it will also improve the efficiency in treatment as I just said if it is more in the therapeutic window then the treatment will be much better. You can also localize the drugs target size, you can prevent unstable drugs to get degraded and again these are some of the studies we can discuss how we can do that. But these are some of the advantages if you have controlled release and long circulation through some engineering aspects.

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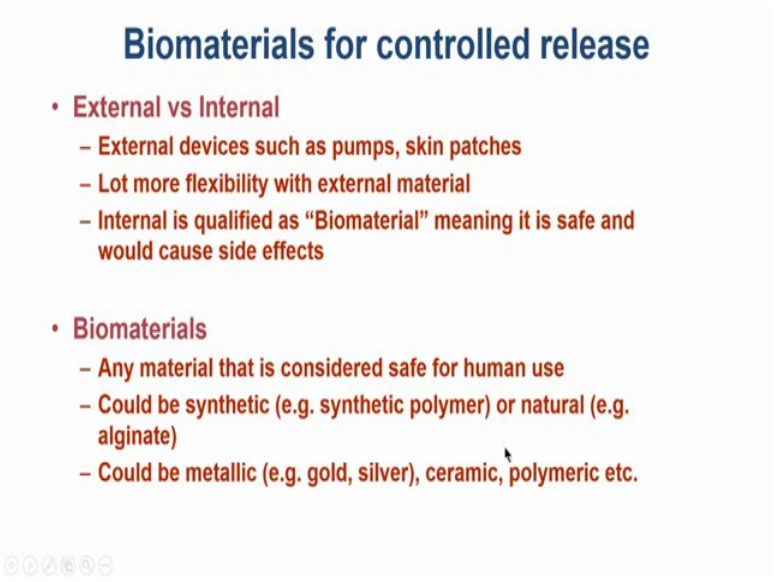

So, another word I am going to introduce is biomaterials. What is biomaterials? Biomaterials is a material that is either being used for biological applications or has been derived from a biological system. So, there can be several types of biomaterials. Hair is a

biomaterial, lots of polymers are being used those are biomaterials. We have stainless steel rods and titanium rods that go into patients body at the time of fractures those can be classified as biomaterial.

So, they can be basically anything that can be used for any application in the body or is derived from the body itself, and these can be both external and internal. So, we can have external biomaterials being used for drug delivery, so you have you might be familiar with the pumps. you might be familiar with skin patches that are put on the skin.

So, those are all external biomaterials there is lot of more flexibility with the material of choice. And the reason for that is since the systems are not going inside the body, the toxicity that they may cause the requirement for them is much less stringent. Because you can get away with the putting something that may not be compatible once implanted in the body, but since it is over the skin is not a big issue.

But if you are going to use internal it has to be extremely safe it should not cause side effect because once it goes inside the body it is not easy to retrieve it and of course, it is going to escalate the cost, it requires a medical practitioner. So, all of those considerations should be kept in mind I mean deciding between external and internal.

So, as I just said any material that is being considered safe for human use can be said as biomaterial these could be synthetic or natural. So, synthetic polymers are used natural polymers such as alginate produced by plants and bacteria could be metallic as I just said titanium and stainless steel gold and silver could be ceramic could be a polymeric material.

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So, let us talk about polymers in a lot more detail then we will continue to do that for the next three or four lectures. So, polymers are everywhere in a daily life, our own DNA is made of very large polymer. We have starch and sugar molecules, cellulose, rubber which we all use in all kinds of vehicles. We have plastics that we are using for our daily groceries and for whatever their applications. The cooking utensils and Teflon is made of them, nylon our clothes that we wear the PVC pipes that we use in our buildings. Polymers are basically everywhere in our daily life.

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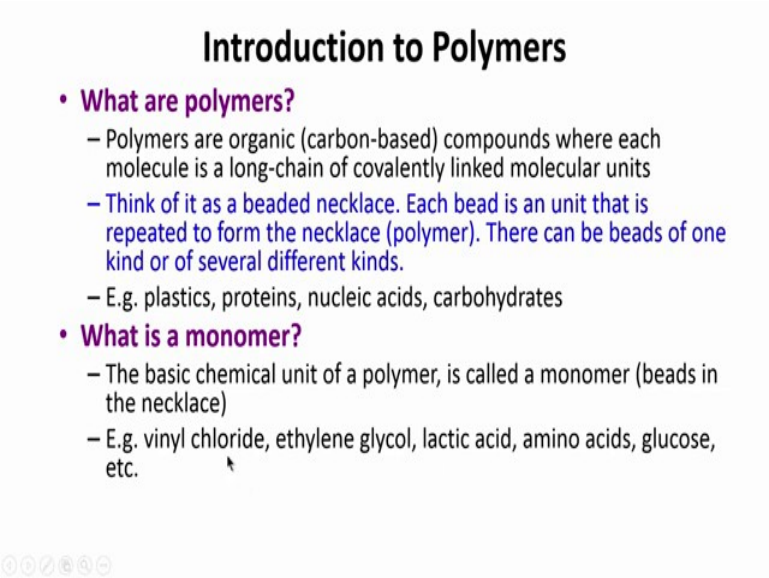

So, let me just introduce some polymers to you. So, what are essentially a polymers? Polymers are organic based compounds, so when I say organic essentially mean carbon backbone based compounds where each molecule is a very long chain which is covalently linked to each other. So, you can think of it as a beaded necklace, so each bead you can say there is a basic unit which has been now linked to form a very long chain. And these beads can be of several kinds, the way the beads are attached can be in several other ways and we are going to talk about those as well.

So, again as I said some examples are plastics, proteins, a DNA, carbohydrates. And what is the monomer? Again, when we talk about polymers, monomers inherently becomes comes into discussion. So, a monomer is a basic chemical unit of a polymer, so which means that these are essentially those beads in the necklace. So, if a polymer is a necklace then the individual beads are the monomers.

So, some examples which are very widely used are amino acids which are found in proteins, glucose again found in all kinds of carbohydrates and sugars. And some synthetic monomers like vinyl chloride and ethylene glycol and we will discuss them again in more detail as we go on.

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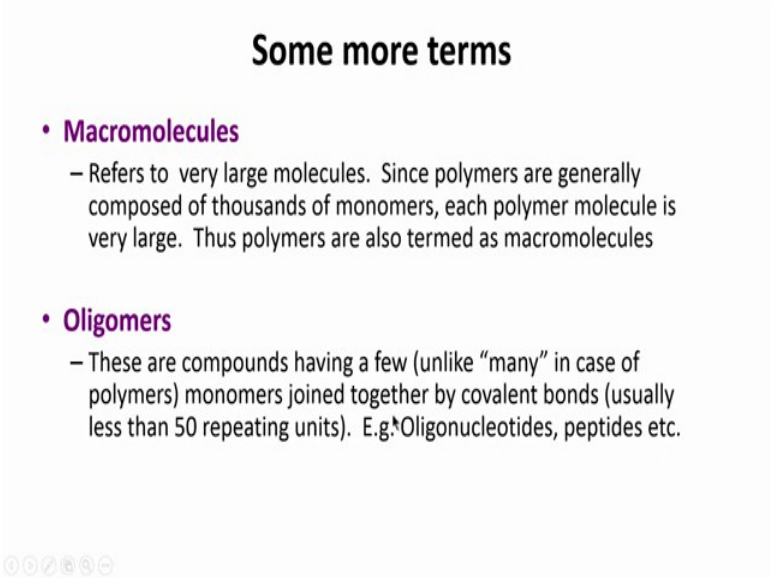

So, some more terms when we talk about polymers. So these can be macromolecules and what essentially is macromolecules? It refers to very very large molecules. These can be composed of thousands of monomers and each polymer molecule is extremely large.

So, thus polymers are also termed as macromolecules, so our DNA is a macro molecule because these can be extremely, long proteins can be extremely long, so those are all macromolecules. Sometimes people use a term oligomers and these are something which are still polymers, but they are not as big of polymers as normally we talk about it in terms of DNA and protein.

So, these are compounds having very few monomers, they are joined together by covalent bonds. So, typically it is called for less than 50 repeating units. But this is again not a consensus, sometimes you will see people talk about other units as well other 20 units or even 100 units as all oligomers. So, small peptides and small oligonucleotides are termed as oligomers.

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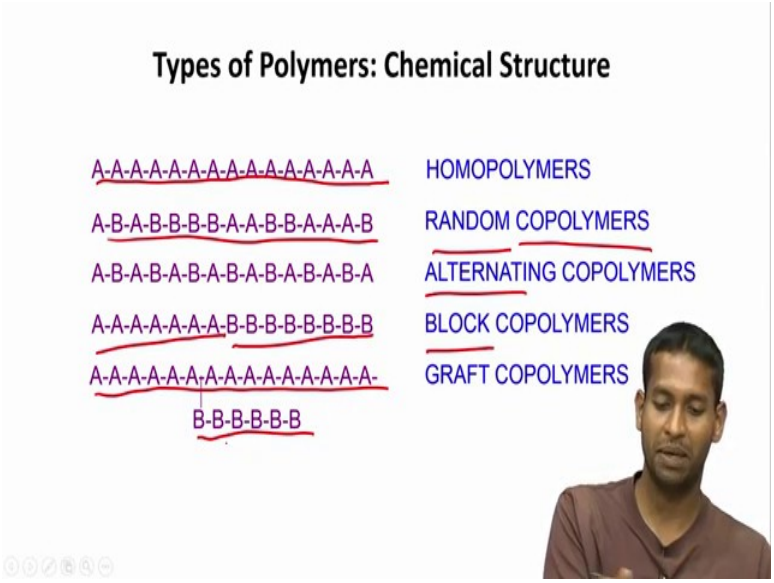

So, what are the different types of polymers, so in terms of the chemical structure. So, you can have a polymer in which there is a single monomer called A which is being connected like this in this format. So, this is one type, so these are called homopolymers, they are called homopolymers because all of the molecules here are the same monomer. You can have something like this in which you have two different monomers, a monomer A and a monomer B which have been covalently cross linked to form a structure which is quite random in terms of the distribution of A and B.

So, these are called random copolymers, so these are copolymers because there are more than one monomer and they are randomly distributed because it could be A B A or B A

B and similarly. And there is really no pattern to this distribution of A and B in this polymer, so they are random copolymers.

A similar class is depicted here, where there is some sort of organization between the two monomers in the polymers. So, these are A B A B essentially meaning that these are alternating copolymer, so this time they are not random, but they are alternating. Or you can have polymers which are kind of segregated with the monomers in general. So, you can have all the As on one side and all the Bs on the other side. So, these are typically called block copolymers because you have a block of A and then a block of B and so that is why they called block copolymers. And then you can have a system where you have the A is continuing throughout the polymer, but then there is a little bit of graft that is added for B which is separate. So, these then are called graft copolymers because in this one, even though by itself I would have made a polymer, but then B is separate and so, it makes a graft here.

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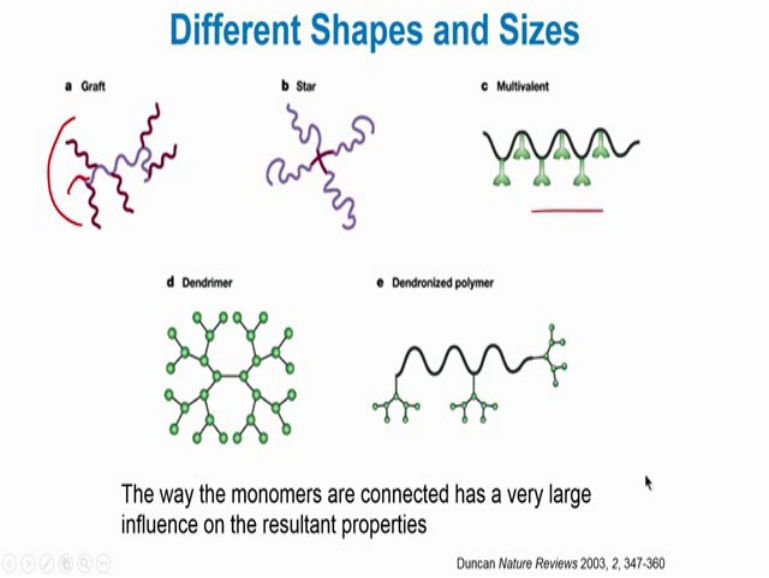

And again they come in different shapes and sizes, so you can have as we just described the graft where you have the polymer main backbone and through which a different things are grafted. They may not be copolymers they might just still be A again, but or they might be multiple types of A B and C or whatever.

So, these are called graft copolymer these can be star shaped and these can be multivalent and these can be dendrimers which depicted like this or this can be

dendronized polymer where is a backbone and the small tetramers are attached to it. So, just the way these monomers are connected has a very large inference on resulting properties and we are going to talk about some of that subsequently.

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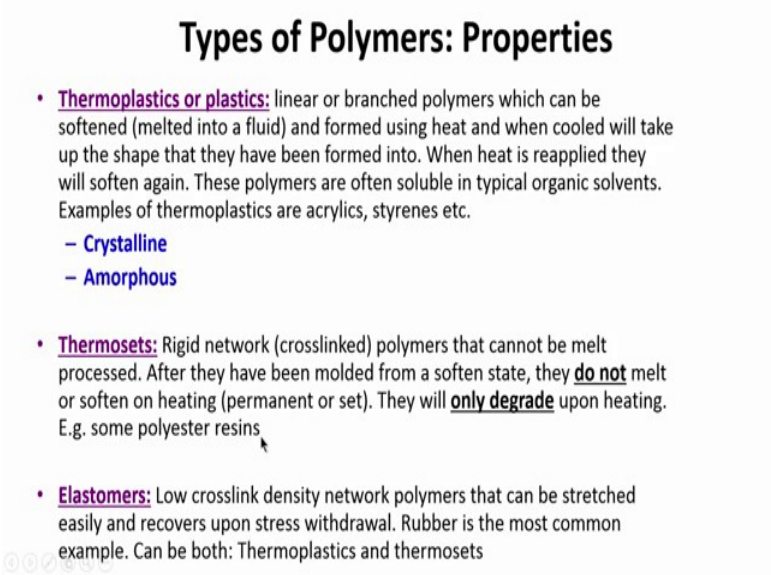

And then polymers can also be defined on the basis of their properties, so there are thermoplastics or just plastics itself. So, these are linear or branched polymers these can be softened typically by heat and when they are cooled they take assume the space or whatever they are softened into. So, they essentially liquid and you put in whatever vial whatever shape vial you want and when means they are cooled they will essentially take that shape.

And these polymers are also typically soluble in organic solvents. So, some of the examples are acrylics and styrene. Further these plastics can be divided into crystalline or amorphous. And again we are going to talk about these two in subsequent classes or these can be thermosets which are essentially the rigid network and they cannot be melt processed once they are formed.

Once they have been formed they cannot be molded down into soften state and they will only degrade once you heat them, so some polyester resins are essentially such classes of polymer. And then finally, we have elastomers these can be both the thermoplastics or the thermosets, but essentially what they are is they are very low cross link density

networks and these can be stretched. So, something like your rubber in the tire is one of the most common examples of such kinds of polymers.

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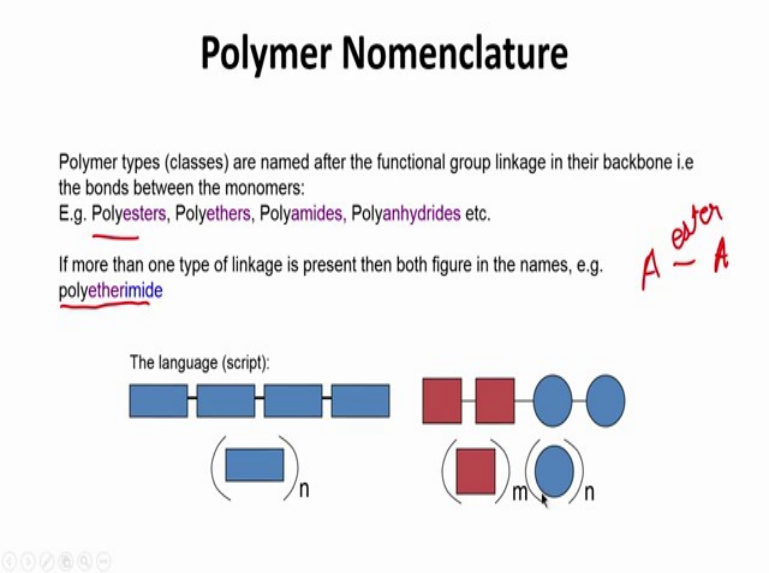

And then finally, for the last slide for today we are going to talk about polymer nomenclature, so polymer types are named after the functional group linkage in the backbone. So, typically let us say if the link between A and A is through an ester bond then they are called polyesters, if this bond is through ether bond it is called polyethers.

So, essentially several of these can be classified into different types of polymers. And there are more type of linkage present sometimes they are even combined, in this case, it is polyether a might. So, it has both ether and amide bonds that are present in the backbone to make these polymers through the monomers. Just a quick note on the language that is being used.

So, typically if you have some monomers let us say n monomers combine to form a polymer it is typically written as monomer times n. Or you can have block copolymers in this case, so you have m units of monomer 1 and then n units monomer 2, so they might be written as monomer 1 m and monomer 2 n.

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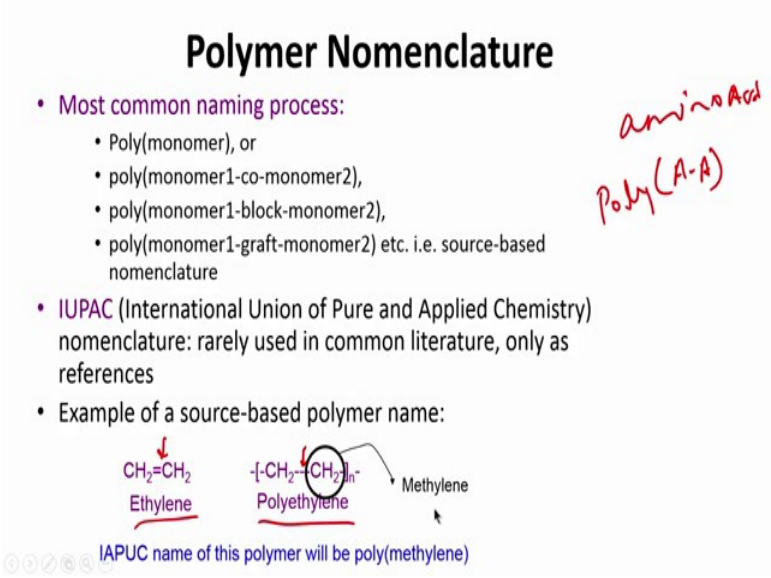

And a little bit on the more polymer nomenclature is, so typically as it just said and they can also be named as poly-monomer. So, let us say if my monomer is amino acid, so I can say the polymer formed from that is poly amino acid, essentially proteins or if there is block copolymers then you can also have polymer monomer 1 copolymer 2 similarly all different kinds of nomenclatures are being used.

So, these are not very standardized. Most of you must be aware with the IUPAC system which is an international way to name a chemical structure. So, these things are rarely used for polymers they are only used for monomers, so just to give you an example. So, you can have ethylene which is a CH2 double bond CH2; however, once is polymerized this double bond is converted to a single bond.

And so, technically it is not really ethylene anymore, but it is still called polyethylene because the original monomer had an ethylene in it. So, these are some of the things we should be careful about when we read through these things. So, this is actually now methylene it is not really at ethylene which is the monomeric unit. But still the IUPAC name for this will be polymethlene, but it is not called polymethlene it is always called polyethylene ok.

So, we will stop right here and in the next class we will continue to learn more about polymers and how they are synthesized, what are their properties. And the reason we are studying all these polymers is eventually we want to use these polymers to make

alternate systems which will allow us to basically tailor the system any numerical system such that we can get into that therapeutic window. So, and see you in the next class.