INDIAN INSTITUTE OF TECHNOLOGY ROORKEE

NPTEL

NPTEL ONLINE CERTIFICATION COURSE

Biomedical Nanotechnology

Lec-17
Nanopharmacology & Drug Targeting

Dr. P. Gopinath
Department of Biotechnology
Indian Institute of Technology Roorkee

Hello everyone I welcome all to these 17th lecture of this course the 17th lecture is on nano pharmacology and drug targeting, so in this lecture we are going to learn what is nano pharmacology.

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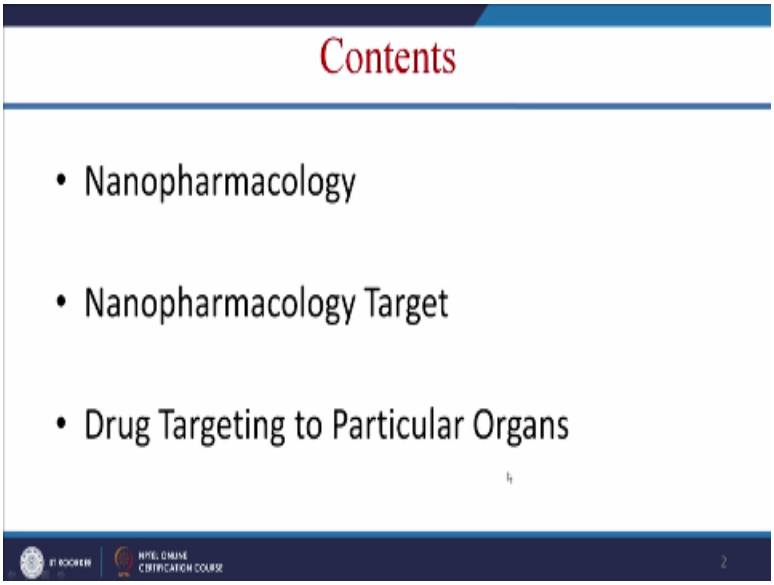

And various nano pharmacology targets and also how to target the drug to a particular organ.

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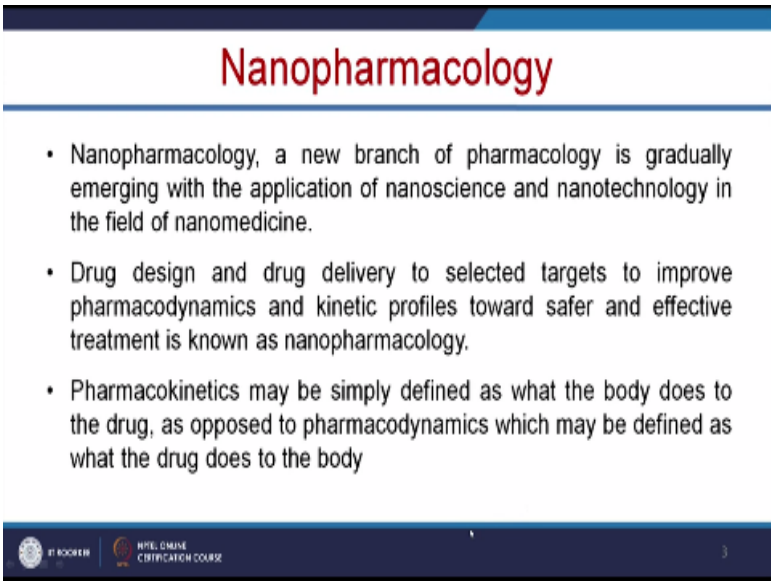

So this nano pharmacology is a new branch of pharmacology and its gradually emerging with the application of nano science and nanotechnology, so let us see the definition of nano pharmacology so it is a drug design and drug delivery to select a targets to improve the pharmacodynamics and kinetic profiles towards safer and effective treatment okay, and let us see the definition between the pharmacokinetics and pharmacodynamics so the pharmacokinetics is simply defined as what the body does to the drug.

Okay, and the pharmacodynamics is what the drug does to the body okay, so based on the pharmacokinetics and pharmacodynamics the efficiency of drug get varied.

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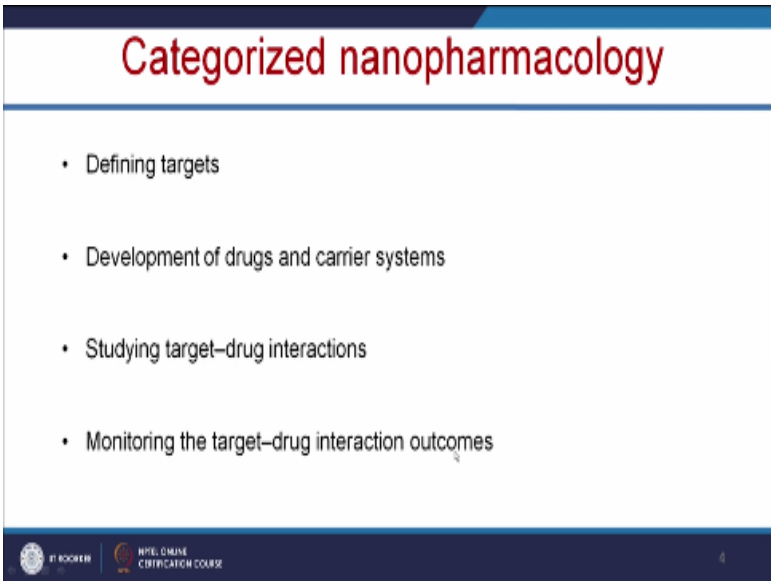

So let us see how the nano pharmacology can be categorized the first one is differing the targets and next one is development of drugs and carrier system and the third one is studying the target drug interaction and fourth one is monitoring the target drug interaction outcomes, so let us see these in detail one by one.

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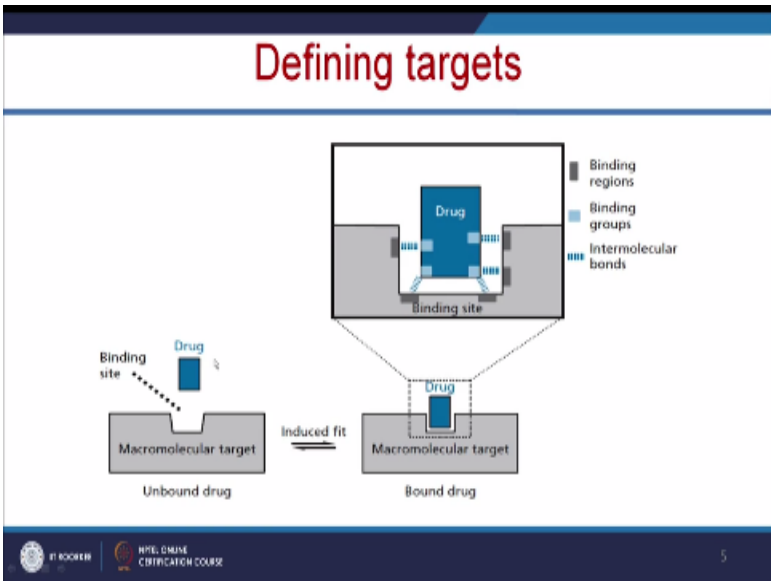

The first one is depending the targets so when you make a drug we should exactly match with the your binding side that is your receptor side, so which is not binding effectively then the therapeutic efficiency will be less. For example so if your receptor is like this.

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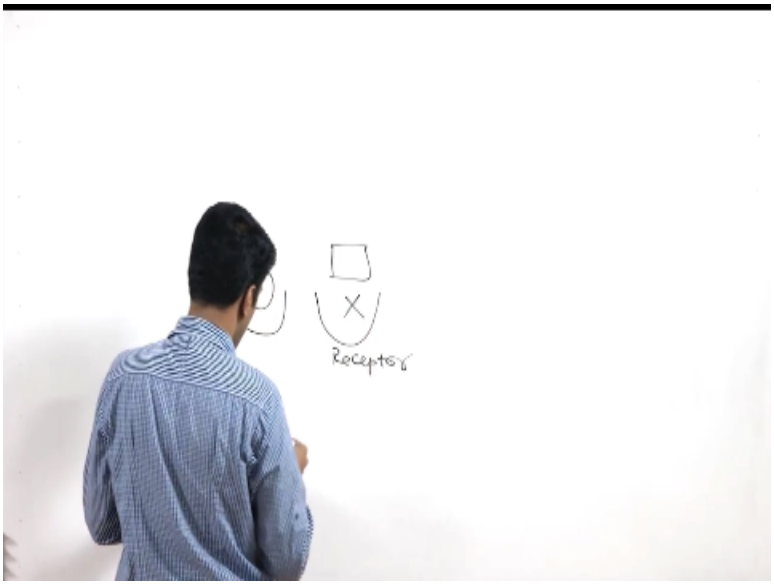

So the drug should go an exactly match with this okay and this is your receptor or a binding side, and if your drug is like this it cannot bind with the binding side so that efficiency will be less if the target is not matching with the drug.

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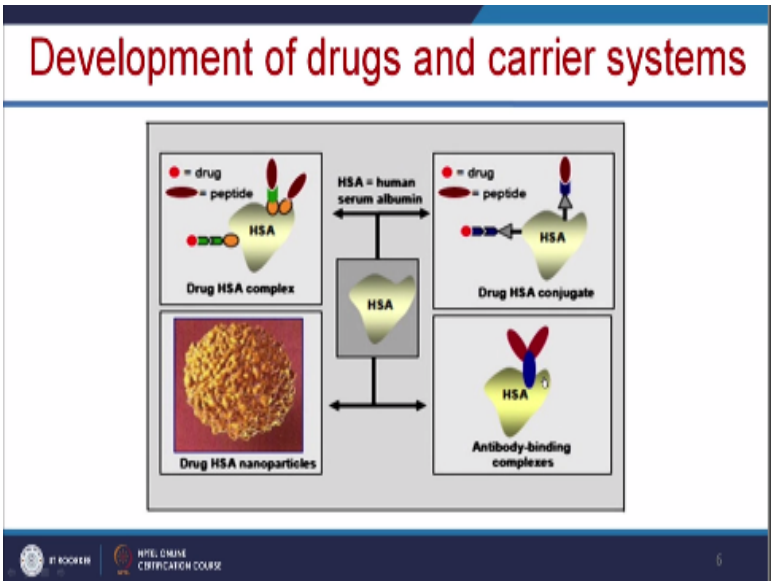

So the next one is development of drugs and carrier systems so we can make a biocompatible and biodegradable and nano carriers which can deliver the drug to the targeted location, for example we can use that human serum albumin so this actual say it is one of the highly biocompatible and biodegradable material okay, and we can load with the any can have drug and also we can target these HAS to the particular location for example if the target is nano particle to the cancer.

We can have the cancers specific antibodies so that it can go and bind only to the cancer cell and it can release the antibodies drug to the cancer cells.

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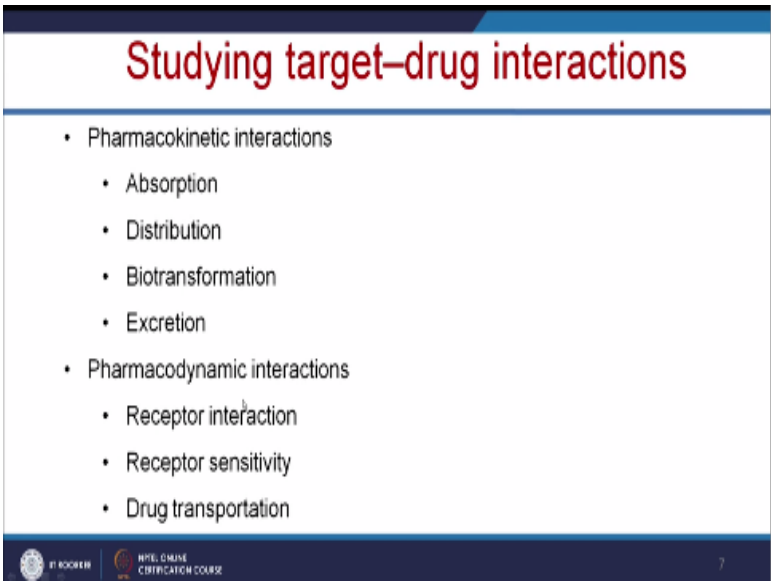

So next one is the studying the target drug interaction, so in case will be learning pharmacokinetic interactions as well as pharmacokinetic interactions as well as pharmacodynamics interactions, so under the pharmacokinetic interaction will be studying the how the drug will be absorbed and what is the distribution and also the biotransformation excretion of the particular drug, and in the pharmacodynamic interactions will be studying how the drug will be interacting.

With the receptor and how if the sensitivity whether it is binding only to the cancer cells or it is binding to the number cell also so those case can be studied and how the drug is transported so these things come under the pharmacodynamic interactions.

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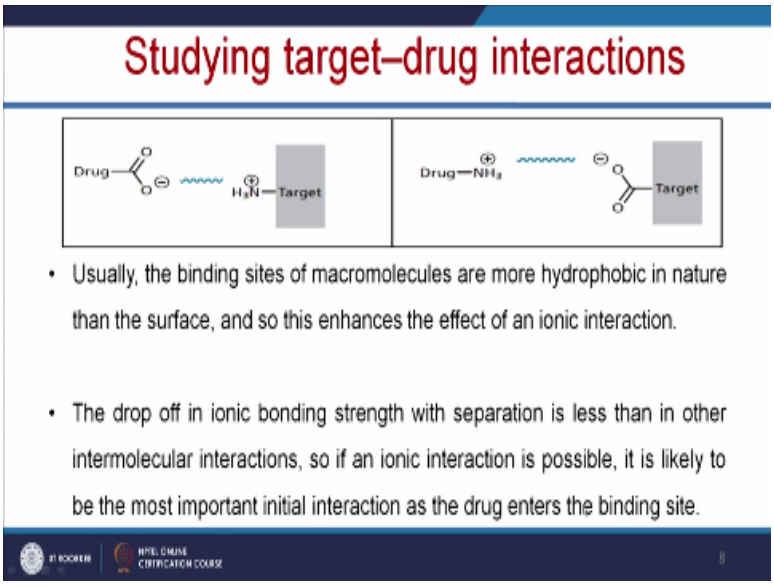

And another important thing is studying the target drug interaction usually the binding size of macromolecules are more hydrophobic in nature okay, so this enhances the effects of an ionic interaction for example if you are having that target with the positive charge and it will be nice if you are have a drug with negative charge it can easily go and bind based on the ionic or electrostatic interactions, and as we know that most of a cells and nucleic acid these have neutrally charge okay.

So when you have the drug with the positive charge it can easily go and bind to the electrostatic interaction, so if an ionic interaction is possible it is likely to be most important initial interaction as a drug enters the binding site.

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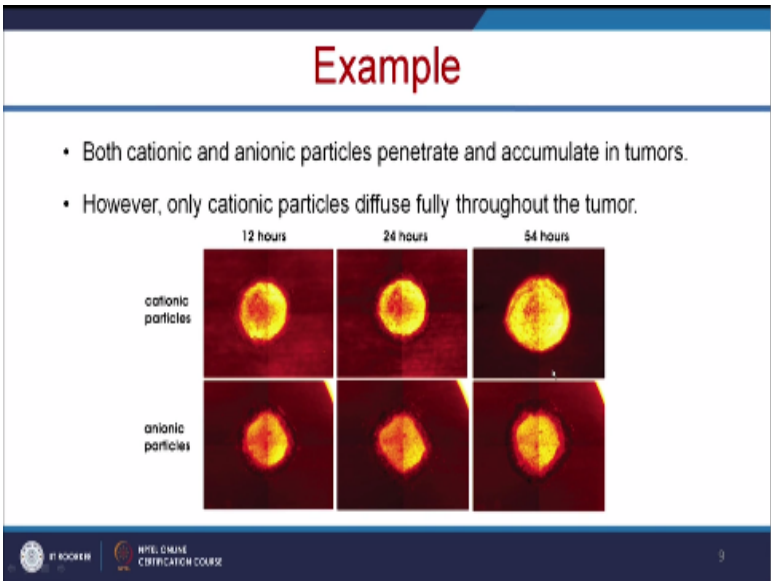

So for example we can see here this cationic and anionic nano particles can penetrate and accumulate in tumors but this cationic particles diffuse fully throughout the tumor, so we can see here so this anionic particles and this is the cationic particles and in the cationic particles it is a fully diffused throughout the tumor and whereas anionic particle it is not diffused properly and compared to the cationic particles.

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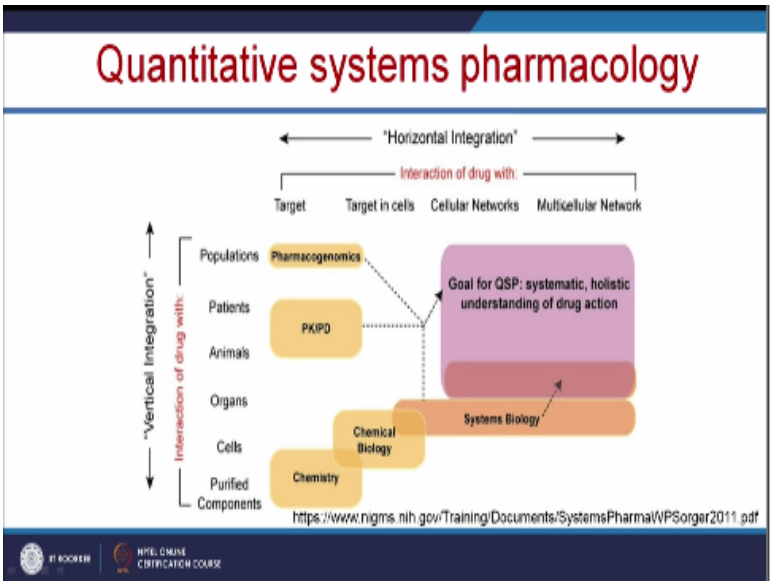

So next important thing is quantitative systems pharmacology so that is QSV so in this will studying the systematic as well as holistic understanding of the drug action, and this is a divided into two categories like vertical integration and horizontal integration okay so here when we make a new drug will be purifying the compounds with the help of chemistry and will be telling the effect of this purified compounds on the cells and then you will study the effect of this drug on the organs.

Then you study these effect of this drug on the animals and patients and then the populations so here in vertical impression we will be studying the interaction of drug with these group okay and in the horizontal integration so you will studying the interaction of drug with the target and how the it will interacting with the cellular networks and also what is the molecular mechanism of the particular drug, so everything will be studying under the horizontal integration.

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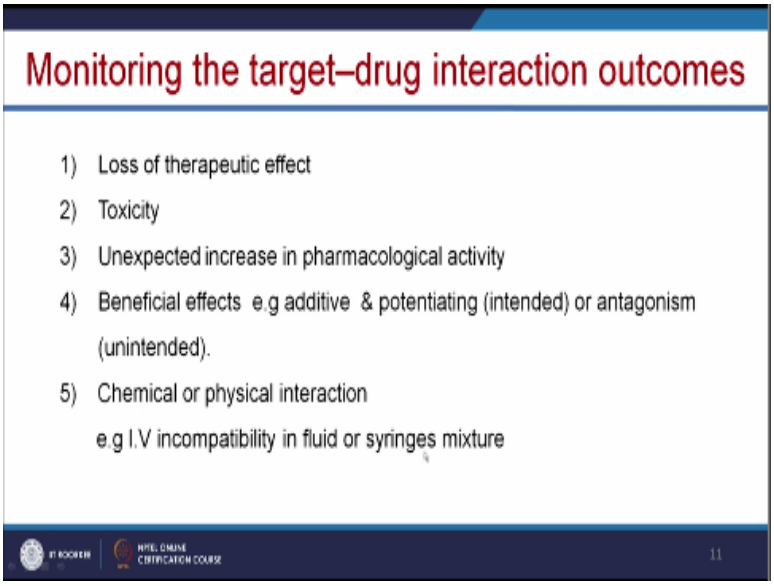

And next one is the monitoring the target drug interaction outcomes okay, so when you give the drug we have to check whether there is any loss of therapeutic effect and what is the toxicity of the particular drug and whether any unexpected increasing the pharmacology activity and for example it may give some beneficial effects for example it can give addictive or sometime it may give antagonism effect and next thing is we have to study the chemical as well as physical interaction for example you have to study whether your drug is compatibility in fluid or syringes mixture.

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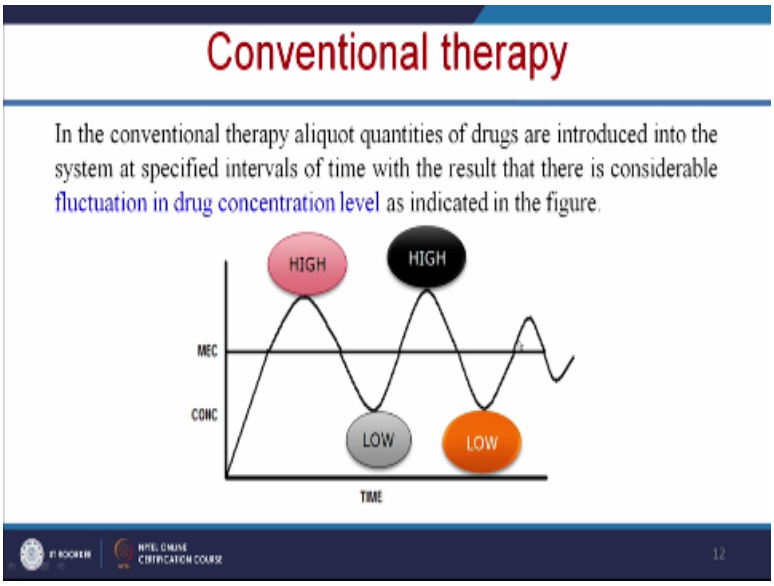

So let us see what is the drawback of conventional therapy so in the conventional therapy so we will be using the particular conventional of drug and that particular concept drug will be taken at specified intervals of time, so due to which what will happen there will be a fluctuation in the drug concentration level we can see here, so the concentration of drug is going high and low.

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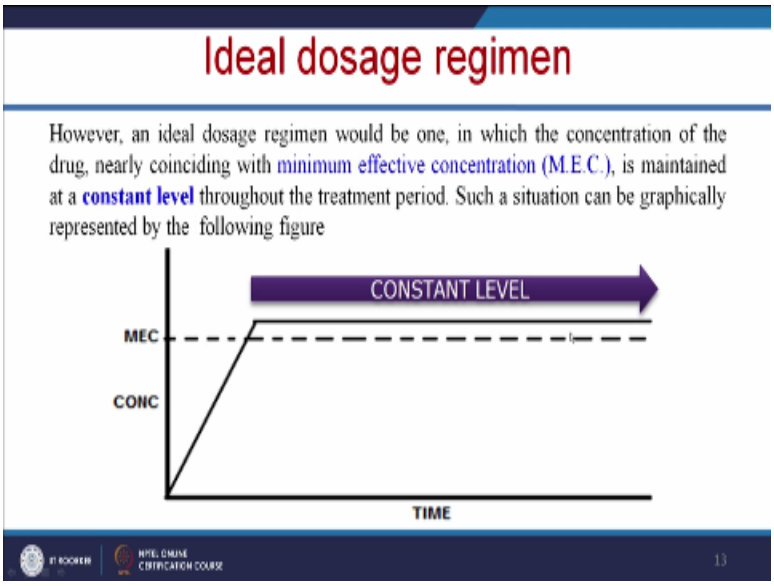

So for an ideal dosage enough to take the concentration which is nearly matching with the minimum effective concentration that is MEC okay and it should be maintain in a constant level throughout the treatment period, so then only the therapeutic efficiency of the drug can be increased.

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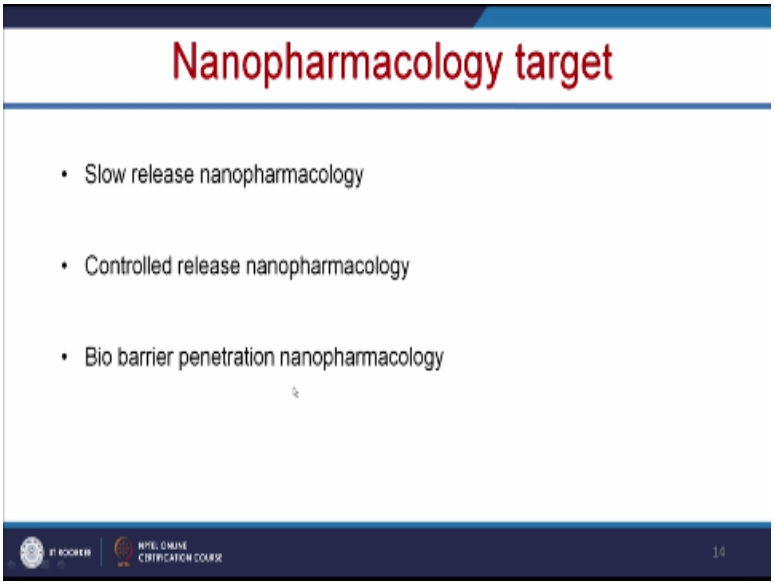

So let us see the various nano pharmacology targets so under this we will be studying about what is slow release nanopharmacology and what is control is nana pharmacology and also will be studying about the bio barrier penetration nanopharmacology.

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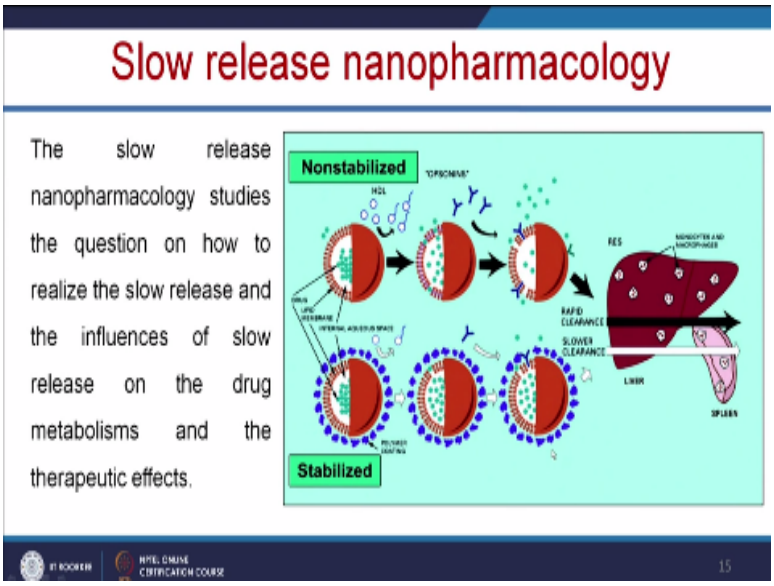

So first we will see what is slow release nanopharmacology so here the slow release nanopharmacology studies the question on how to realize the slow release and influence of slow release under drug metabolism and therapeutic effects, so we can see here there is a non stabilized carrier so where the drug is releasing very rapidly so when the drug is released in more concentration what all happen is like a it will removed by your reticular endo theory system so it will be removed by the liver as well as spleen.

And in case of stabilized carrier you drug will be released very slowly okay and we can see here it can slowly release the drug and it can stain the blood stream for more time.

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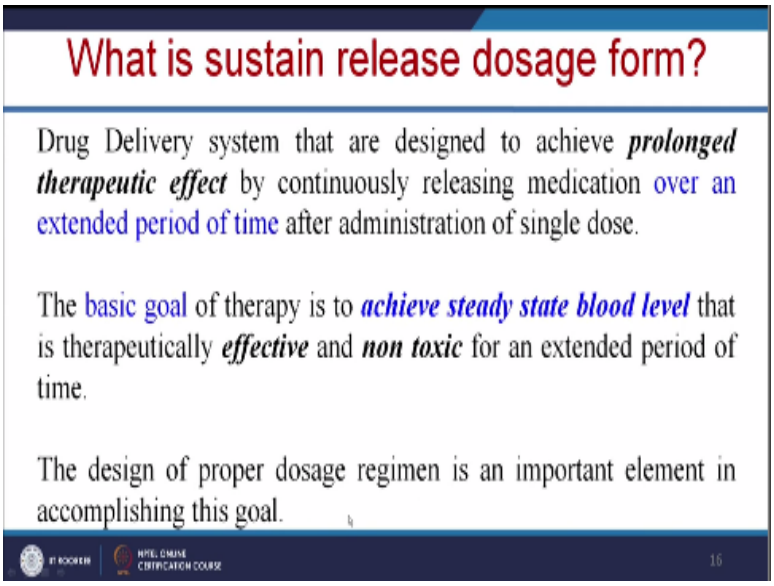

So before we study the control is nanopharmacology let us see what is sustain release dosage form okay so here that drug delivery system that are design to achieve prolonged therapeutic effect by continuously releasing the drug or an extended period of time okay after administration of single dose and the basic goal of the therapy is to achieve steady state blood level that is therapeutically effective, and non toxic for an extended period of time, so the design of proper dosage regimen is an important element in achieving this goal.

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So let us see the different between the control release and sustain release so the control delivery is then which deliver the drug at a pre determine rate for a specified period of time that is called as control drug delivery, and here the control release is perfectly 0 order release okay that means the drug release over time it is irrespective of concentration, and in case of sustain release it is different as type of dosage form in which a portion of the drug that is initial dose of drug will be released immediately.

And in order to achieve the desired therapeutically response more promptly okay, so initially the drug will be released immediately to achieve the desired therapy effect more promptly and then the remaining drug that is maintain those that will be released slowly and there be achieving at therapeutic level which is prolong and but not maintain constant level okay, so this sustain implies slow release of drug over a period of time and it may or may not be controlled release.

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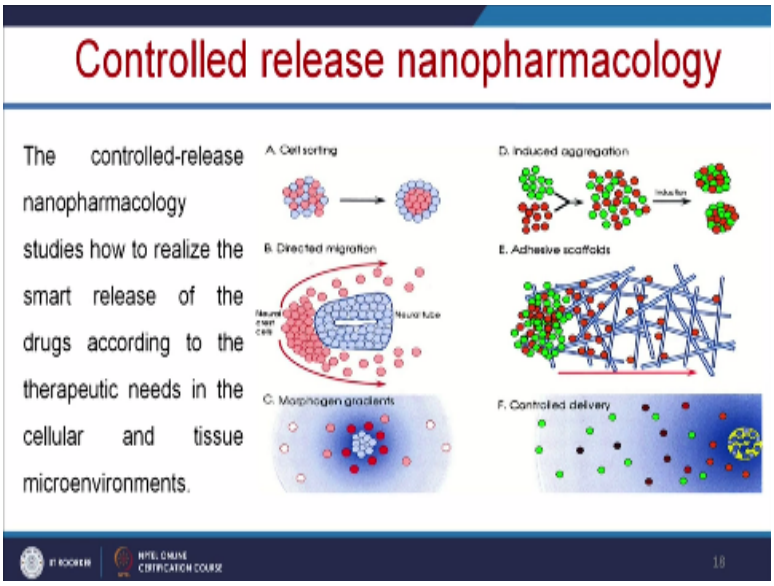

So let us see the control release nanopharmacology so here the controlled release nanopharmacology studies how to realize this smart release of the drugs according to the therapeutic needs in the cellular and tissue microenvironments so can use a smart nano carrier for example we can make a smart nano carrier which can release the insulin depends on the blood glucose level if there is a more blood glucose level it can release the insulin from the smart nano carrier system.

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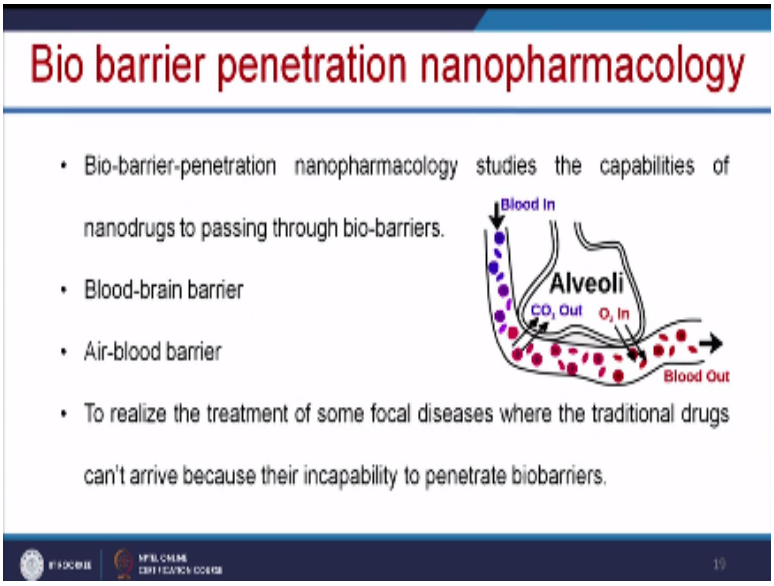

So the next one is bio barrier penetration nanopharmacology, so here the bio barrier penetration nanopharmacology studies the capabilities of nanodrugs to passing through the bio barriers, so the two important bio barriers is blood brain barrier and other one is air blood barrier, okay so to realize the treatment of some diseases where the traditional drugs cannot reach because of the incapability to penetrate these bio barriers.

So we can use the nano carriers which can easily cross the blood brain barrier and it can deliver the drug and which could be useful for various therapeutic applications.

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So let us see what really happens when you take a drug, so this is a patient group and same diagnosis and same prescription but you can see here different kind of effects, so to particular group the drug may be toxic but it is beneficial to other group the drug is toxic and not beneficial and to the other group the drug is not toxic and not beneficial and to other group it will be not toxic and beneficial.

So where to study the effect of the drug to different patient groups before we take it for commercial application, so here the question is can we predict the drug efficacy and toxicity and can we reuse the old drugs or can we design the personalized medicine for the particular patients need.

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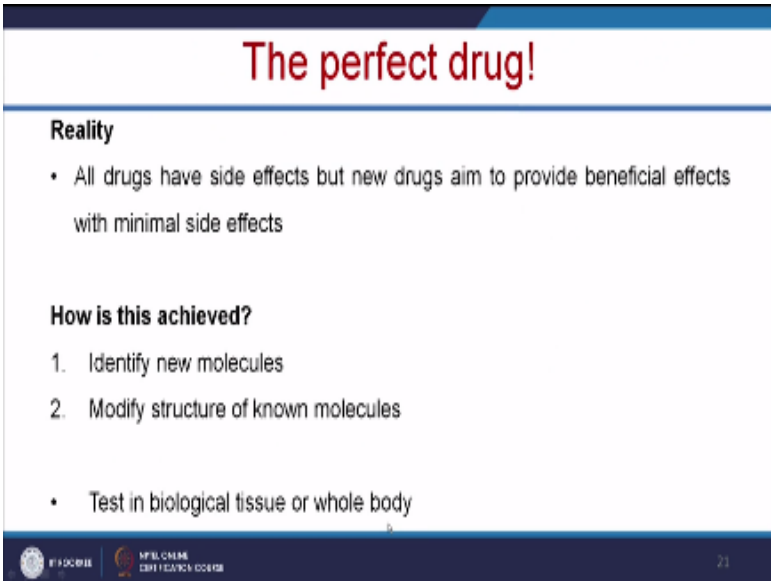

So what is the perfect drug okay, so here the all drugs have side effects but new drugs aim to provide beneficial effects with the minimal side effects okay, so it can be achieved so by identifying a new molecules or modifying the structure of the known molecules and testing these in the biological tissue or the whole body.

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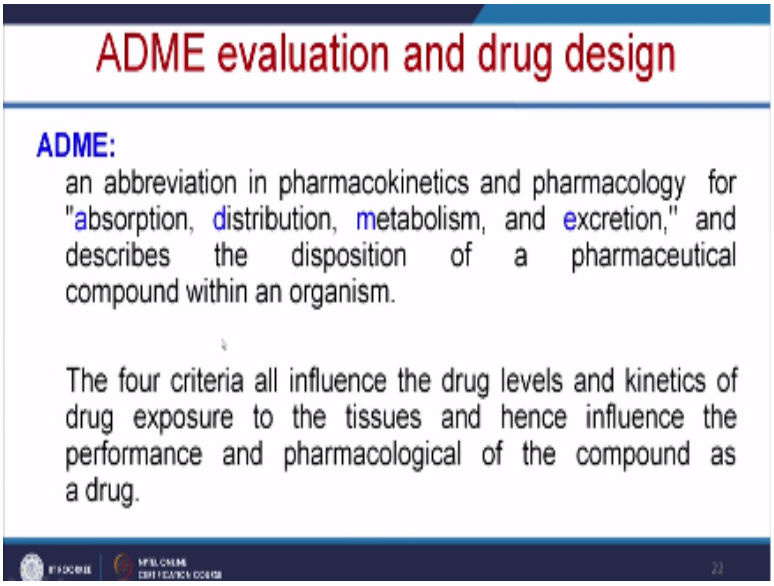

So if you make any drug, so first thing we have to do the ADME evaluation okay, so based on that we have to design the drug. So what is ADME evaluation so ADME means so it is a abbreviation in pharmacokinetics and pharmacology for absorption, distribution, metabolism and excretion so how the drug will be observed, how it is distributed in the body and what is the metabolism and how it will be excreted from the body, okay.

And this four criteria influence the drug levels and kinetics of drug exposure to the tissues and thus it influence the performance and pharmacological of the compound as a drug.

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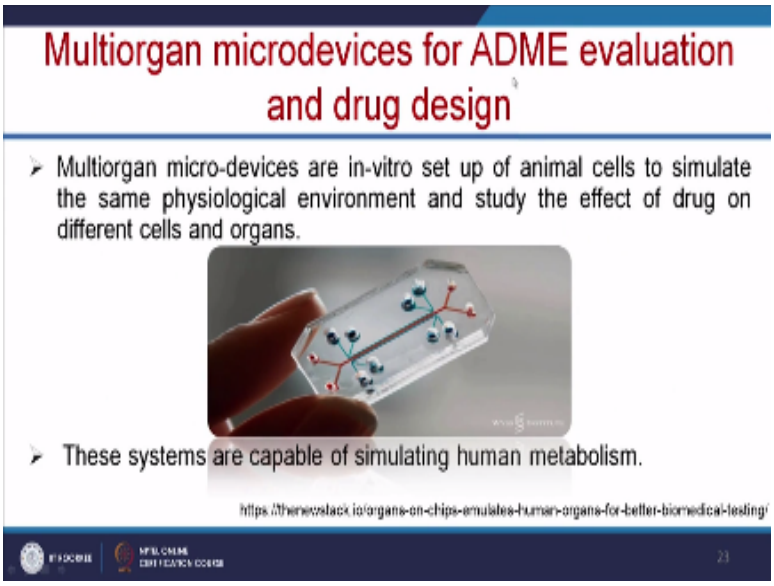

For ADME evaluation we can use the multiorgan microdevice instead of using the animal model okay, so we can use this multiorgan microdevice so this multiorgan microdevice are the in vitro set up of animal cells to stimulate the same physiological environment and study the effect of drug or different cells and organs. So here these system are capable of stimulating the human metabolism.

So this is like a organ on a chip or human on a chip so this chip will mimic like your human metabolism, so we can add that drug into this chip and we can study the effect of the drug on the particular organ.

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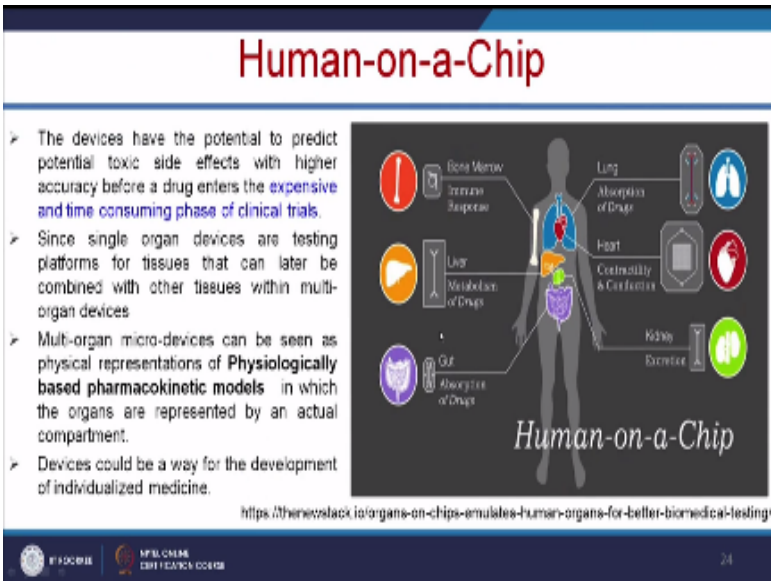

So you see here this example of human on a chip, so we can make this kind of chip we will study how the drug will be excreted okay, so this is like a kidney on a chip and next to one is we can also make a gut okay, so and we can study how the drug will be observed and also we can the liver on the chip and we can study the metabolism of drugs and we can make a bone marrow on the chip and that will tell you the what can a remainder spots it will the drug will induce, okay.

So here the devices have the potential to predict the potential toxics side effects with higher accuracy before a drug enters the expensive and time consuming phase of clinical trials. So before we take the drug to the clinical trial which is time consuming and expensive so we can use this lab on a chip or human on a chip and we can study the effective of this drug on this then we can take it for that for the clinical trial and commercial applications.

So since the single organ device are testing platforms for tissues so that can be later be combined with other tissues within multi organ devices and here the multiorgan micro devices can be seen as the physical representation of physiologically based pharmacokinetic models in which the organs are represent by an actual compartment, okay. So and this devices could be a wave for the development of individualized or personalized medicine.

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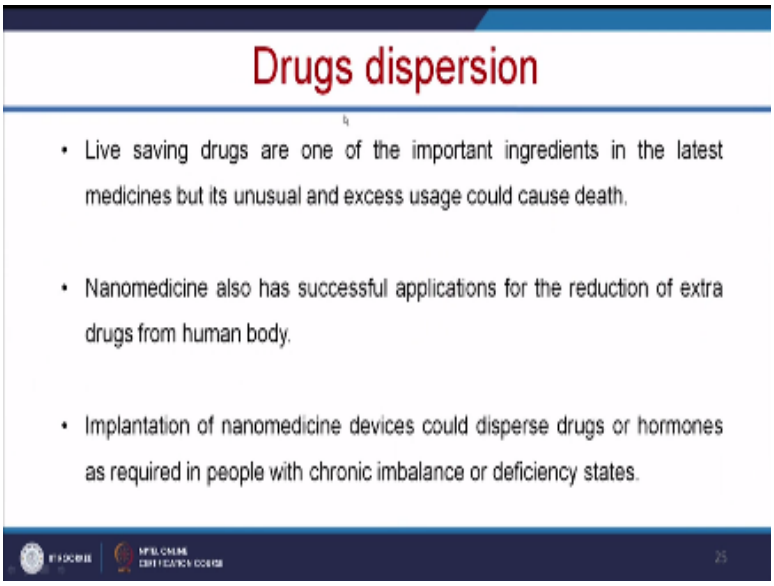

So let us see the drug dispersion, so here the live saving drugs are one of the important ingredients in the latest medicines but it is unusual and excess usage could cause death. So the nanomedicine has a successful applications for the reduction of extra drugs from the human body and implantation of nanomedicine and devices could disperse drugs or hormones as required in people with chronic imbalance or deficiency states.

So this nanomedicine or nano carrier it can act like a small dilute system and according to the need of the patient it can release the drug and it can save the person from the particular disease.

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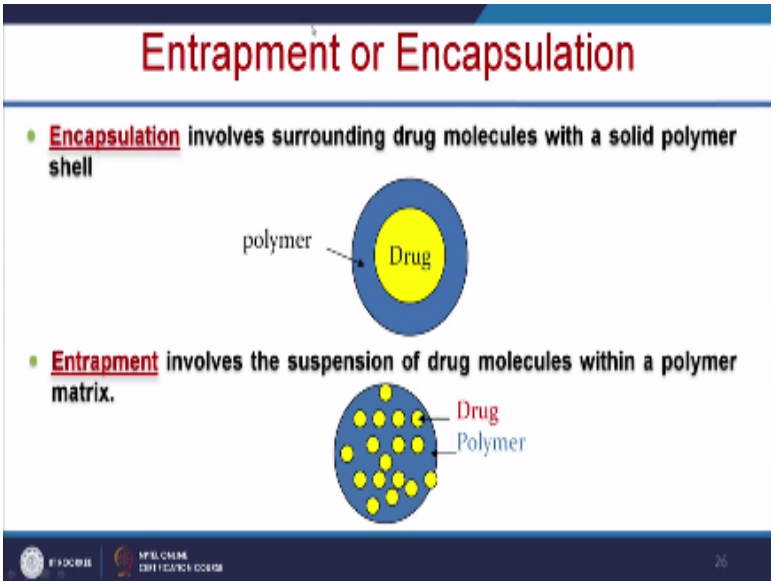

So let us see the difference between entrapment and encapsulation of drug so encapsulation of drug means it involves a surrounding the drug molecules with a solid polymer shell okay, so this yellow color is your drug and it is surrounded by a polymer and entrapment means it involves the suspension of drug molecules within a polymer matrix, you can see this yellow is a drug and this blue color is a polymer. So the drug is entrapped between the polymer matrix.

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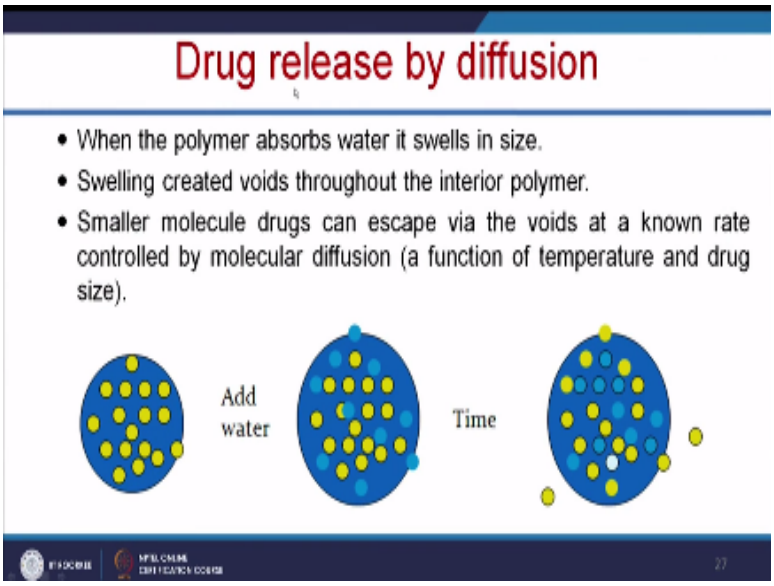

So let us see that drug release by the diffusion so when the polymer absorbs water it swells in size okay, and this swell in created avoids throughout the interior polymer and the smaller molecules can escape through the voids at a known rate controlled by molecular diffusion okay. So when you put this nano particle into water so it will swell and it will release the drug slowly, and we can control the release of this drug by simple cross linking reaction.

So based on the cross linking, so we can control the release of the drug, we can he want more release of drug at initial stage we can do it or he want to release the drug slowly that also can be possible.

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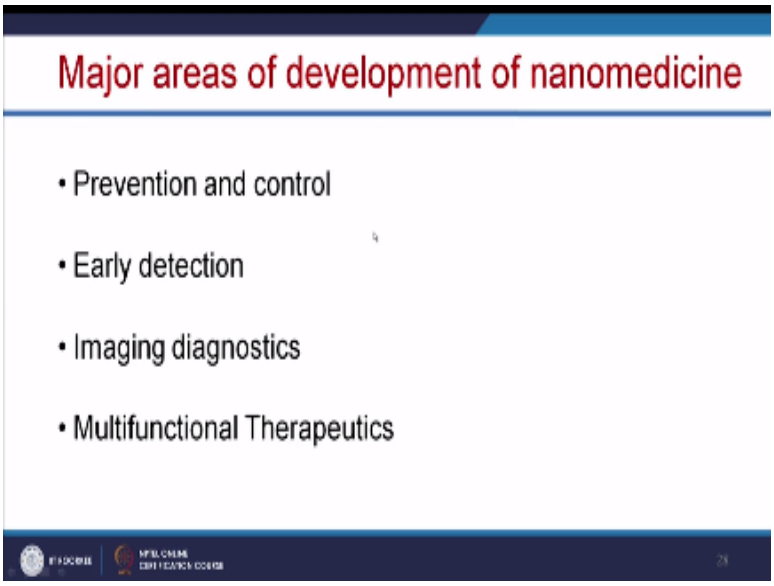

And the major areas of development of nanomedicine is prevention and control and by using this nano materials we can early detect any disease and also we can use it for very diagnostic application and also we can make a multi function nano materials which can do the diagnostics as well as therapeutics simultaneously.

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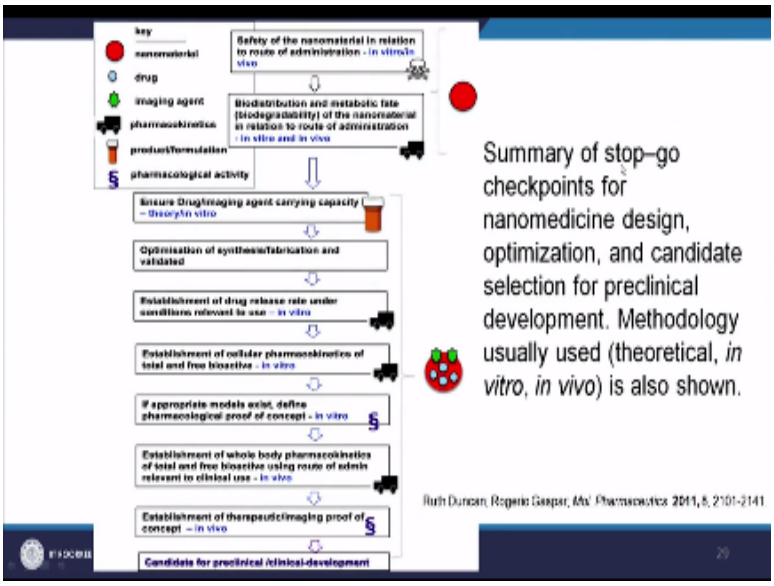

So let us see these summary of check points for nanomedicine design and optimization okay, so before we take this nanomedicine for clinical application we have to cross all these steps. So first thing is we have to study the safety of nano material in, in vitro, in vivo and we will be studying the bio distribution in, in vitro and in vivo and we have to make sure that what is that drug and imaging agent carrying capacity, it can be theoretical or it can be in vitro studies.

And you will be studying the drug release rate in vitro and we will be studying the effect of this drug on the cells then you will study the effect of this drug on the animal model and human applications in a particular group okay, so then you will be taking it for commercial applications. So each and every drug has to cross through all those steps okay, so then only it can reach the market for commercial application. So that is why each and every drug it is taking at least 10 to 15 years to reach the market.

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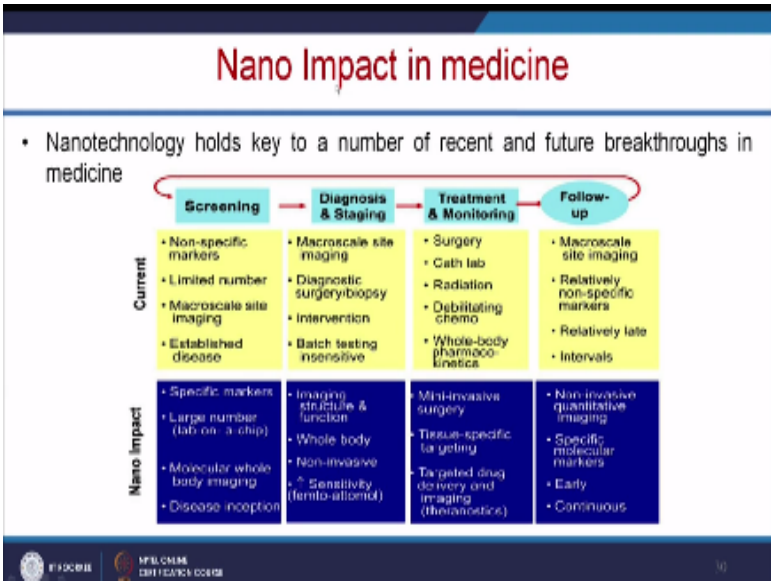

So let us see the impact of nano in the medicines okay, so let us see the compression between the current strategies as well as nano strategies, so if you want to screen a particular disease by using the current methodology there may be a chance for non physics markers and when we use the nano material we can go and buy only to the specific markers and here we can do limited number of test but here we can do the large number of test using this lab on a chip and in case of diagnosis like macro scale site imaging by using the current methodology.

But here we can use the whole body as well as it can be non immersive, in current strategy we have to go for immersive technology okay, and here in case of treatment we have to go for surgery or radiation okay, and whole body pharmacokinetics and here we can reduce that surgery it can be minimal immersive or we can make a drug which can derived to the particular target okay, so the target delivery is possible.

And again for follow up we have to use the macro scale site imaging and here then when you use the nano we can use the non immersive qualitative imaging and we can also do the early diagnosis under early follow up.

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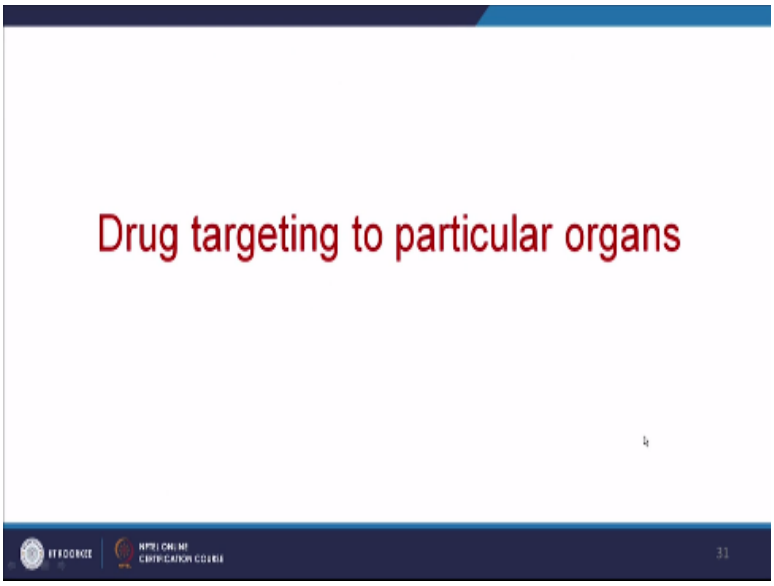

So let us see how we can target this drug to a particular organs.

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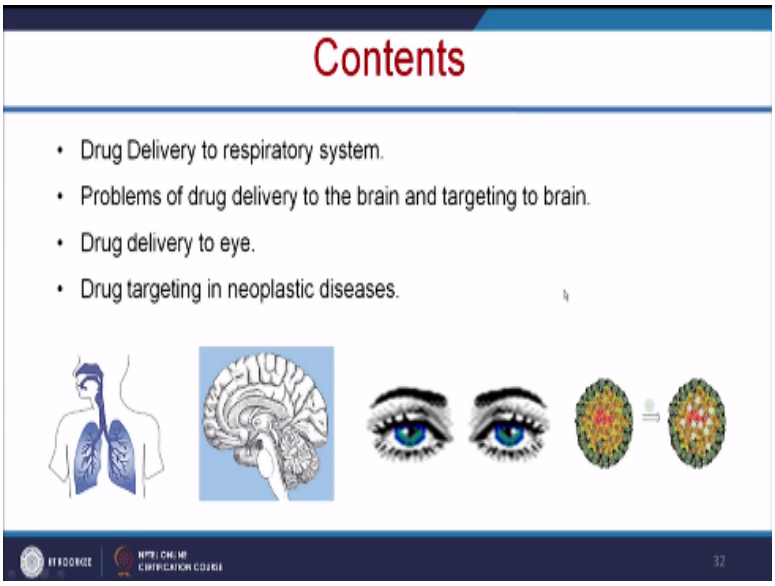

So under this we are going to see how we are going to target this drug to the respiratory system and how we can target the drug to the brain and how we can target drug to the eye as well as the neoplastic diseases.

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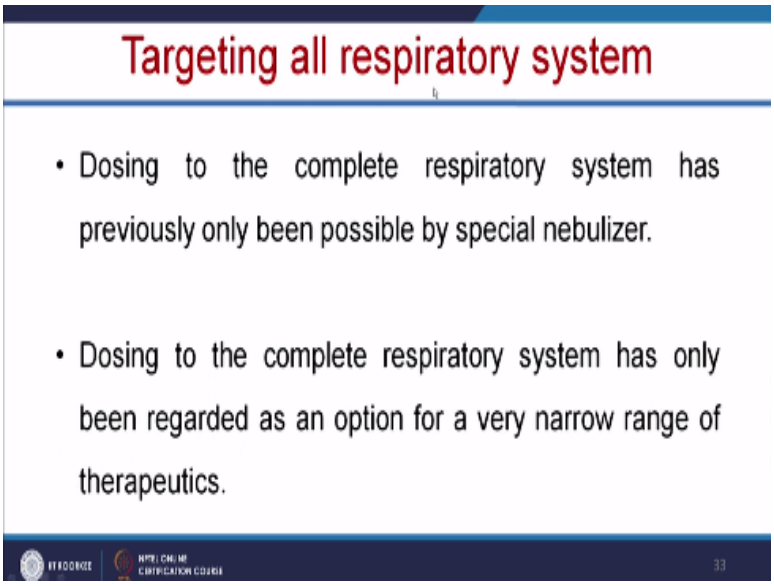

So let us see how we can target the drug to the respiratory system the dosing to the complete respiratory system was possible previously by a specialized nebulizer and dosing to the complete respiratory system has only been regarded as option for a very few narrow range of therapeutics, so some of the disease we have to deliver the drug to the respiratory system directly, okay. So in those cases we can make a inhalable nano particles or micro particles so that can reach their respiratory system and it can deliver the drug.

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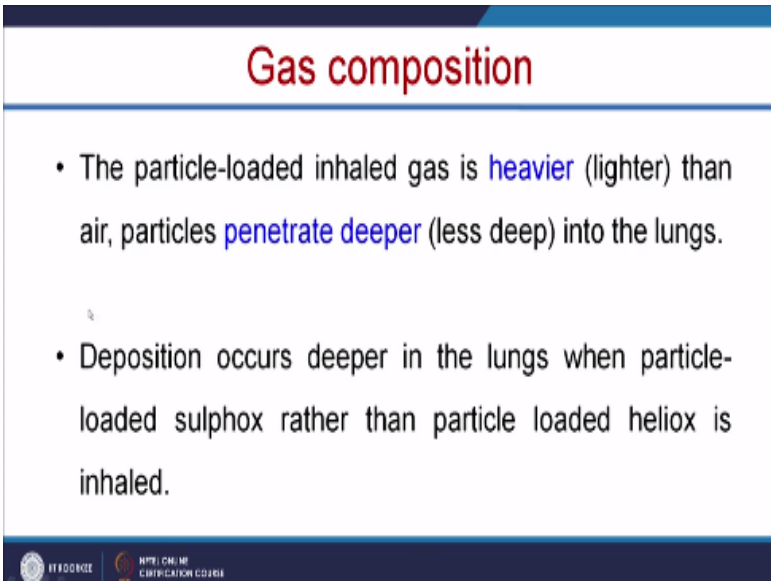

So here the particle loaded inhaled gas is if it is heavier it can penetrate deeper in the lungs and if it is lighter it can penetrate less deep okay, for example the deposition occurs deeper in the lungs when particle loaded with sulphox drug okay, when compared to the heliox drug.

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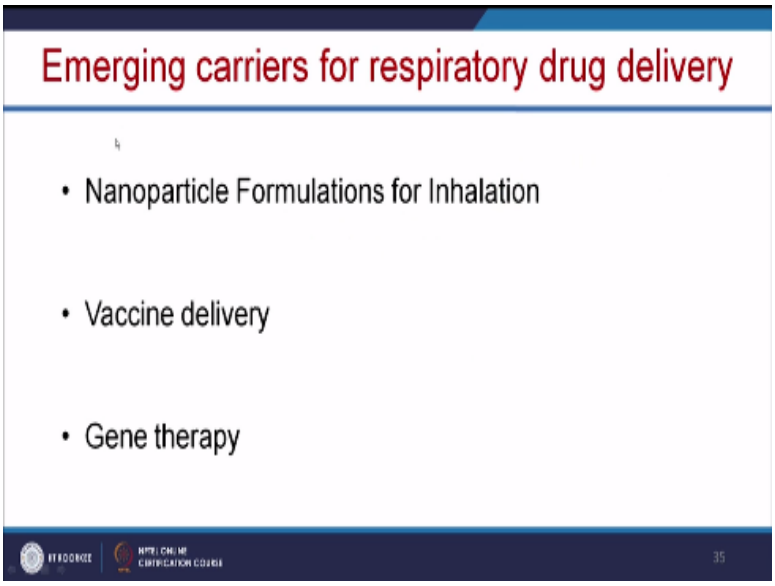

So we can make this nano particle formulations for vaccine delivery and gene therapy and also for various other drug delivery applications, so we can make the inhalable nano particles.

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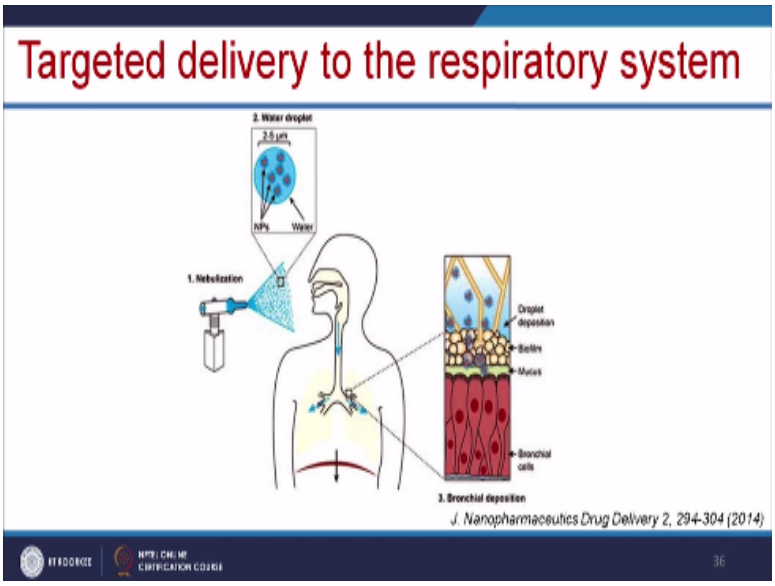

So let us see how we can deliver the drug to the respiratory system so using the nebulizer we can deliver this inhalable nano particles to the person and this can reach the lungs and it can deliver the drugs.

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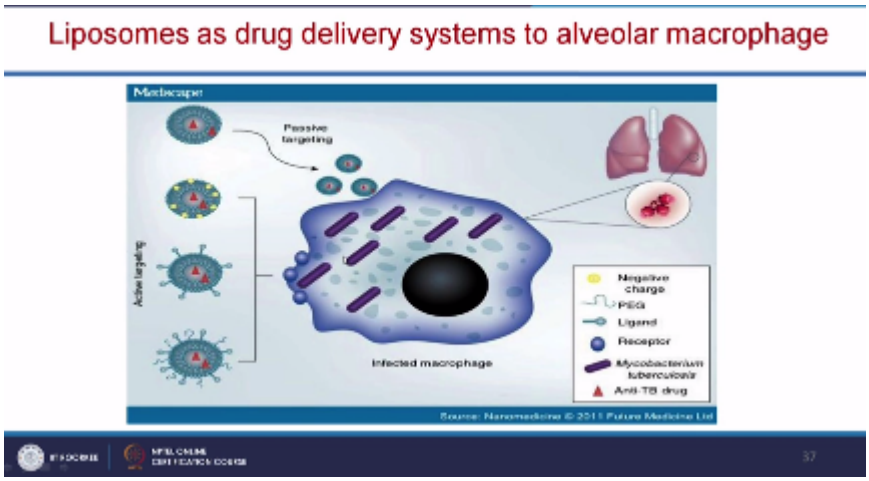

For example it can be used for the lung cancer or other lung related diseases, so we can use for micro bacterium tuberculosis therapy. So you can have the little based carriers or polymeric nano carriers, which can reach the lungs and kill the micro bacterium tuberculosis.

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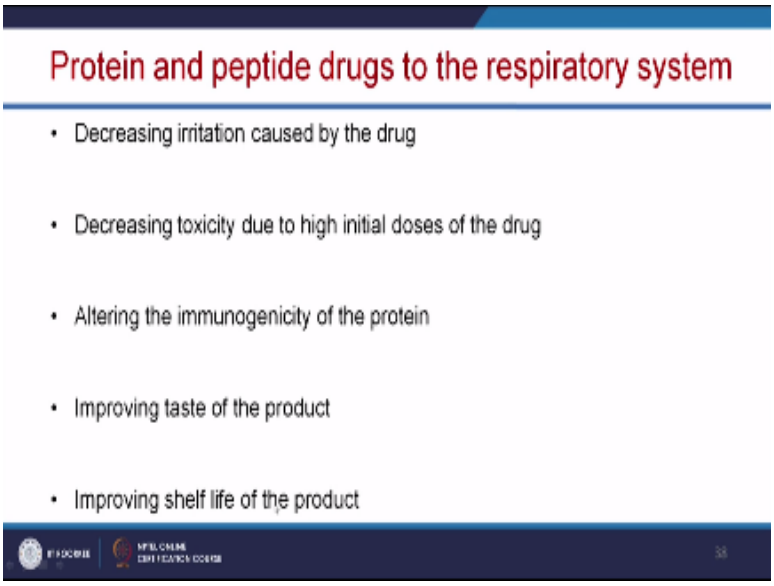

And we can also have the protein and peptide based drugs to the respiratory system, so that is the decrease the irritation cause with the drug and also it will decrease the toxic to high initial doses of the drug and also it will alter the immunogenicity of protein and also improve the taste of the product and also it will improve the shelf life of the product.

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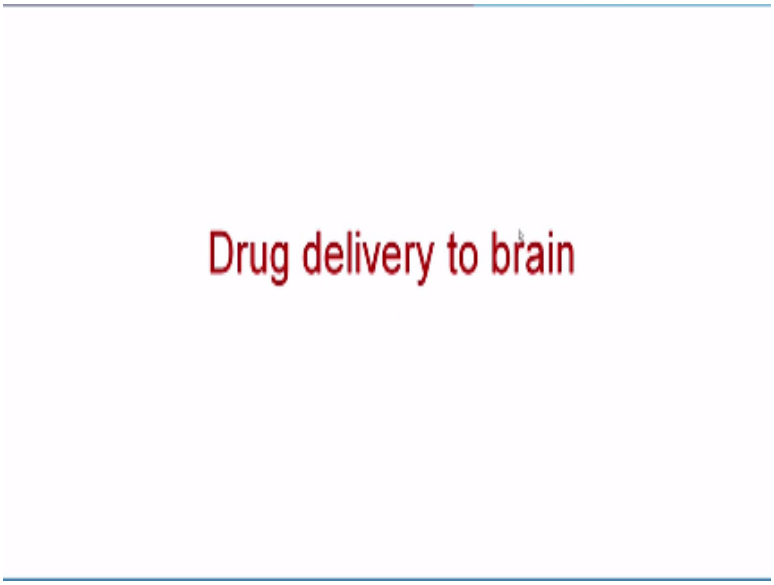

So let us see how can we deliver the drug to the brain.

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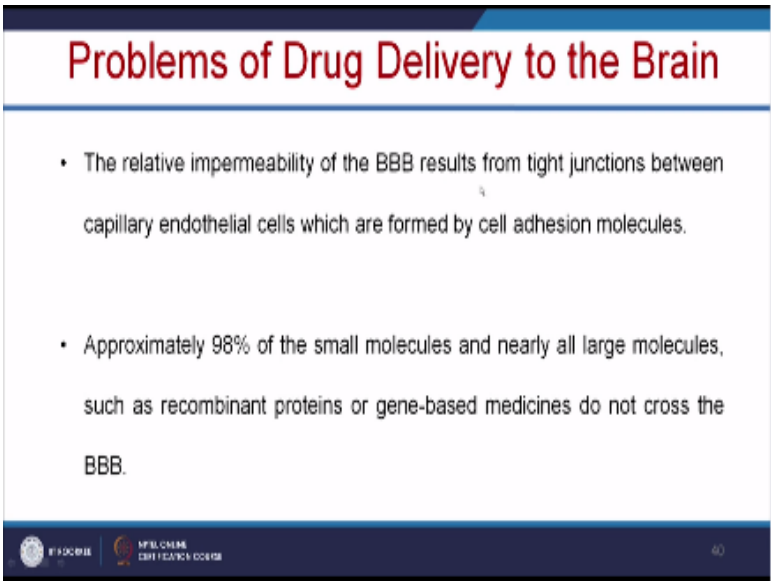

So the problems of drug delivery to the brain is like, the relative impermeability of the blood brain barrier, due to the tight junctions in the capillary endothelial cells which are formed by the cell adhesion molecules and approximately 98% of the small molecules and nearly all large molecules, such as recombinant proteins or gene based medicines do not cross the blood brain barrier. So that is the major problem for delivering drug to the brain, so most of the drugs it cannot cause the blood brain barrier.

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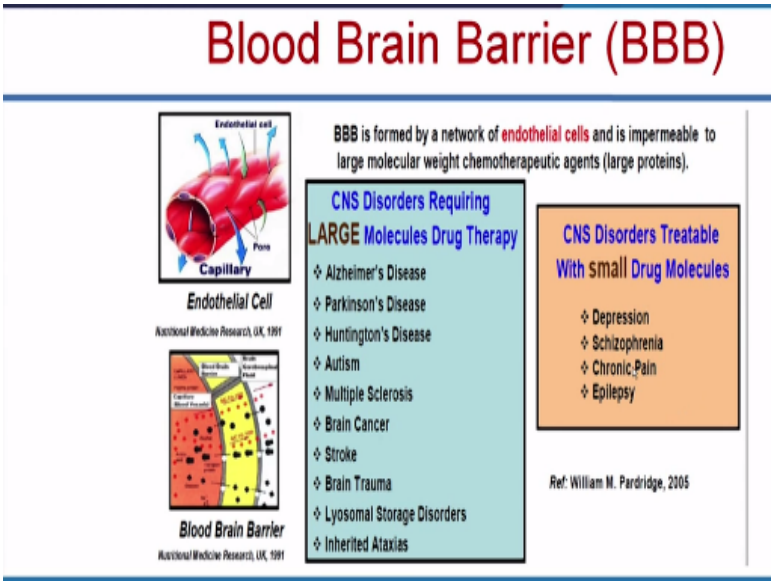

So this blood brain barrier is formed by the network of endothelial cells as I told you earlier and it is impermeable to large molecular weight chemotherapeutic agents. So what are the diseases that we have to send the drugs to the brains? For example CNS disorders requiring the large molecules drug therapy is, Alzheimer disease, Parkinson disease oaky, and other disorders which need which need small drug molecules like depression, schizophrenia, chronic pain, so these things need a small drugs molecule.

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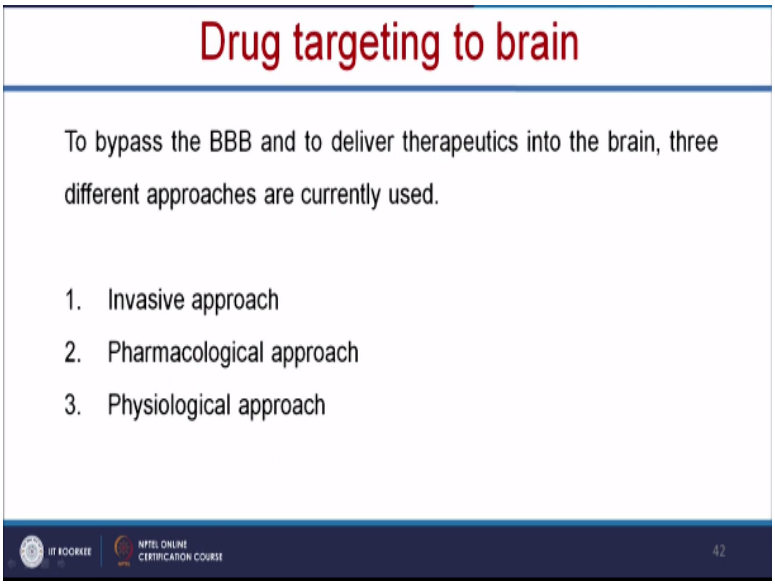

So let us see how we can target the drug to the brain, to bypass the blood brain barrier therapeutics into the brain, three different approaches are currently used, first one is invasive approach, the next one is pharmacological approach and the physiological approach.

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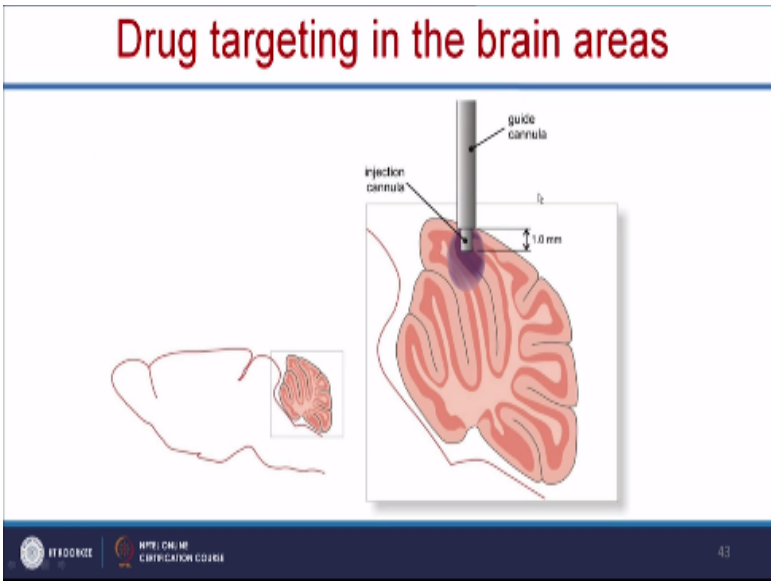

First one is invasive approach; we have to inject the drug directly to the brain.

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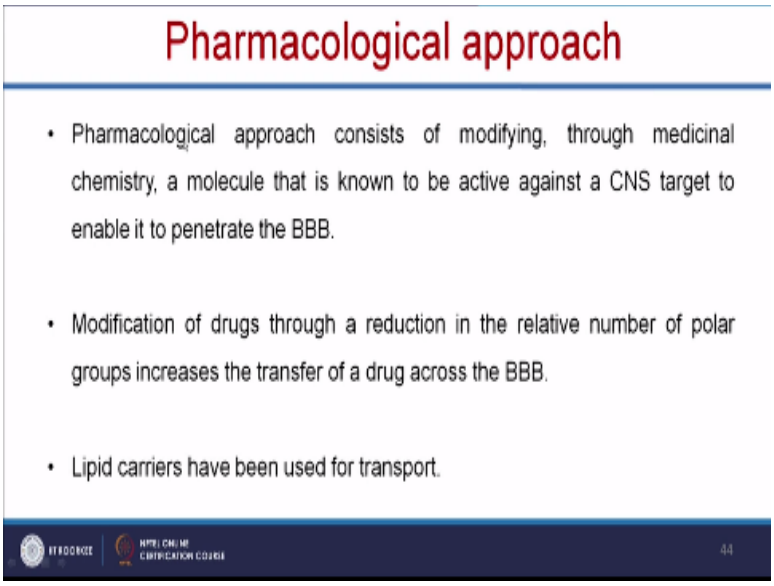

So let us see the pharmacological approach is consists of modifying through medicinal chemistry, a molecule that is known to be active against a CNS target to enable it to penetrate the blood brain barrier and here the next one is modification of drugs through a reduction in the relative number of polar groups increase the transfer of a drug across the blood brain barrier. So here the mostly the liquid carriers have been used for the transport to the blood brain barrier.

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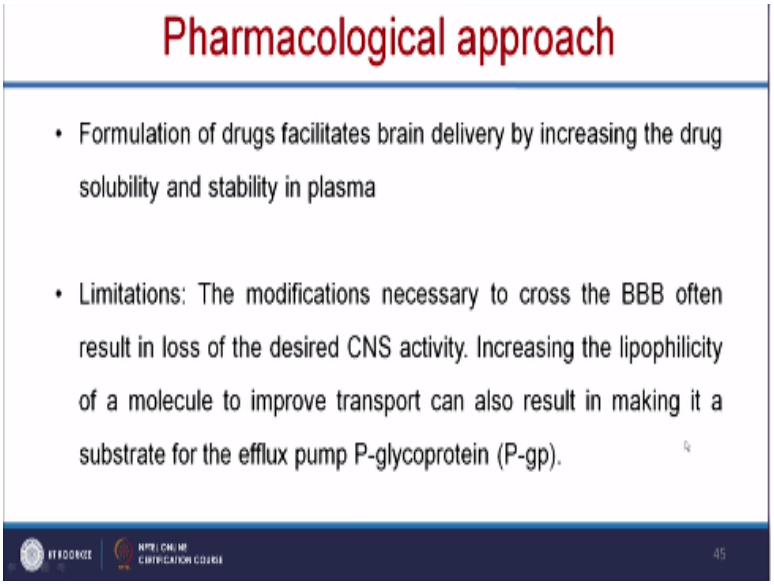

So here in the pharmacological approach like formulation of drugs which facilitates brain delivery by increasing the drug solubility and stability in plasma but the limitations are the modifications necessary to cross the blood brain barrier often result in loss of the desired CNS activity and increasing the lipophilicity of a molecule to improve transport can also result in making it a substrate for the efflux pump P glycoprotein. Okay so when you modify the drugs, causing the blood brain barrier, what happens is? It may lose is therapy activities or it may be remove by the P glycoprotein form.

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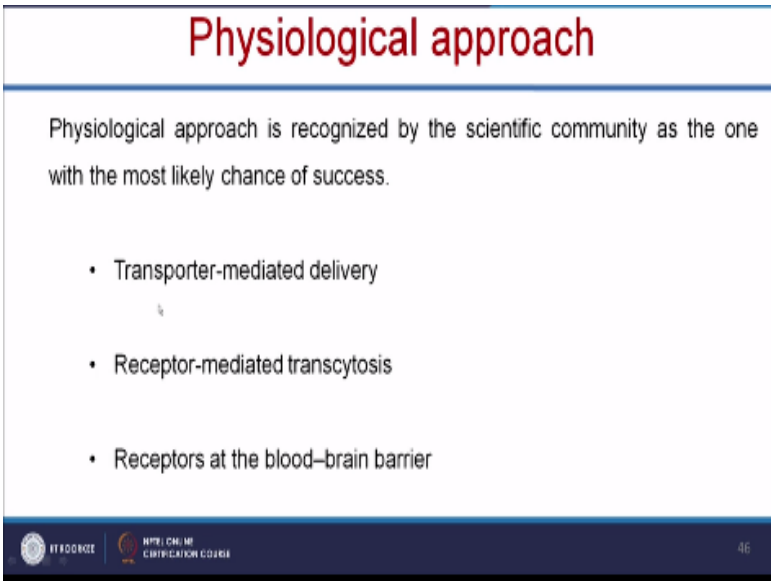

So let us see the pharmacological approach, pharmacological approach is recognized by the scientific community as the one with the most likely chance of success, so here the drug will be delivered to the brain region by transported mediated delivery, and receptor mediated transcytosis and the receptors at the blood brain barrier.

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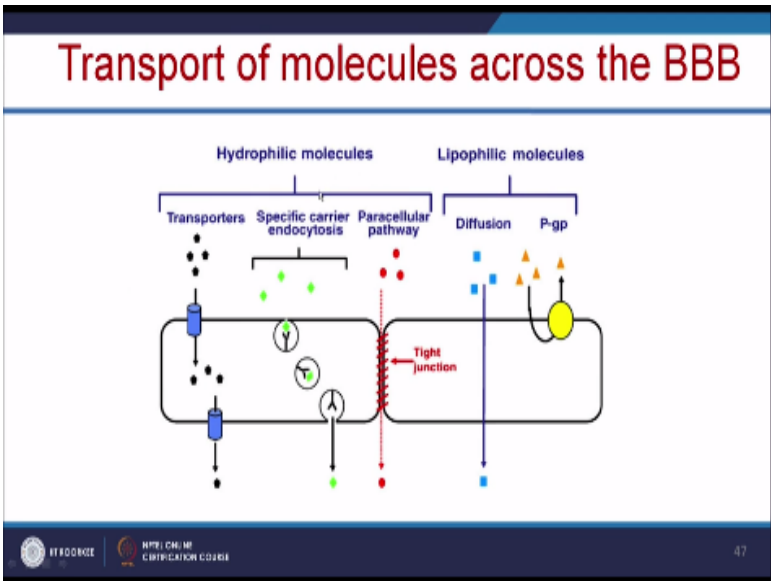

So you can see here hydrophilic molecules can cross the blood brain barrier using this transporter or specific carrier endocytosis or it can be the para cellular pathway and the lipophilic molecules can simply diffuse the blood brain barrier.

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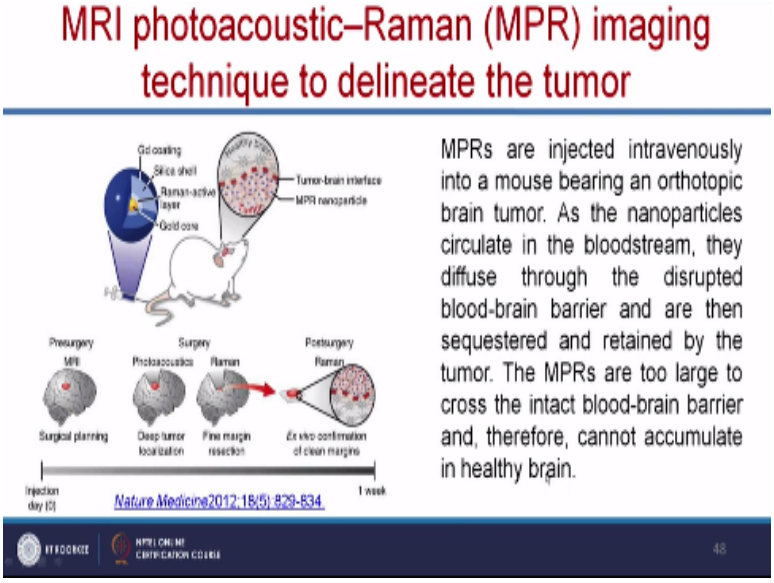

Let us see an example hoe these nanoparticles can be used for imaging the brain tumor, so this is the MRI photocoustic Raman imaging technique to delineate the tumor. So these nanoparticles are injected into a mouse bearing an orthotropic brain tumor and these nanoparticles can circulate in the blood stream and it diffuse to the disrupted blood brain barrier and that will be retained by the tumor and this MPR is too large to cross the intact blood brain barrier, so it cannot be accumulated in healthy brain.

And you can see here these MRP is made of gold core and the Raman active layer and followed by you are having this silica shells and top you are having the gd that is coating. So by using these nanoparticles the imaging of brains can be done in three levels like, pre surgery MRI, surgery and also post surgery also.

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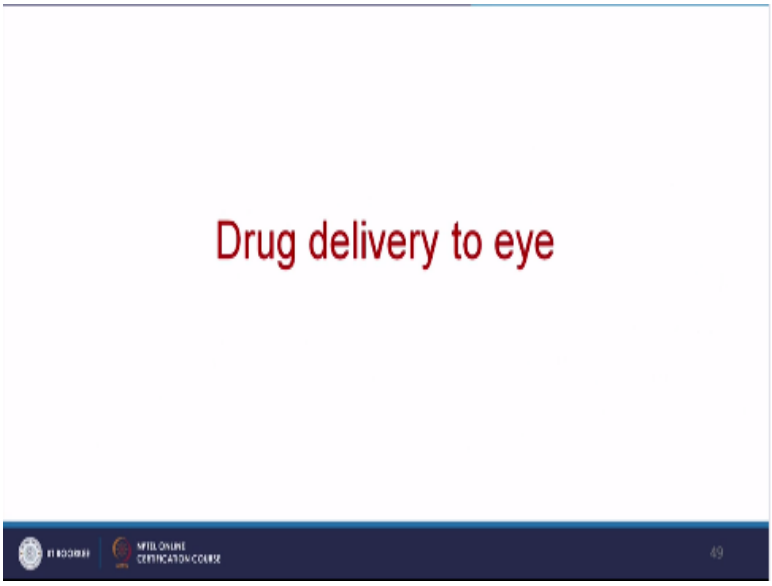

So let us see how we can deliver the drug to the eye.

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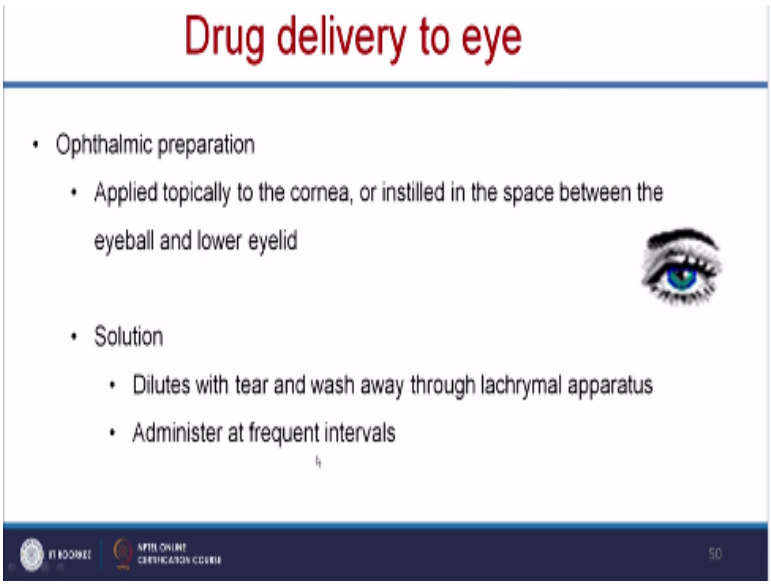

So in the ophthalmic preparation, it can be applied topically to the cormea, or instilled in the space between the eyeball and lower eyelid okay, so we can use the solution, but the problem is dilutes with tear and wash away through lachrymal apparatus and we can also administer at frequent intervals.

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And we can use the suspensions it will longer contact time and it may cause irritation due to the particle size of the drug ad in the ointment and again in the longer contact time and grater storage stability and it may produce the film over the eye and blurring vision.

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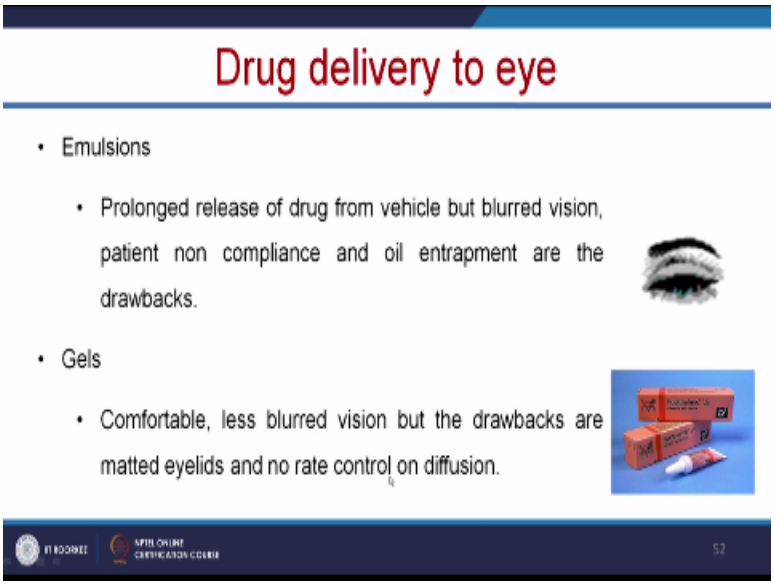

And we can use the emulsion for the better view here it can have the prolonged release of drug from the vehicle but blurred vision, patient non compliance and oil entrapment are the drawbacks and we can also use the gels it is comfortable less blurred vision but the drawbacks are matted eyelids and no rate control on diffusion.

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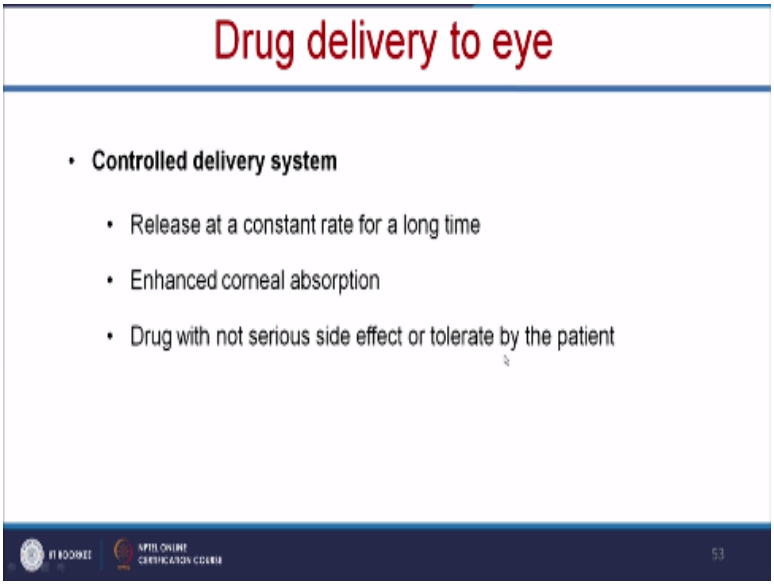

So we can have the nano carriers which will have the controlled system, so it will release at a constant rate for a long time, enhanced comeal absorption and also the drug with not serious side effect or it can be tolerated by the patient.

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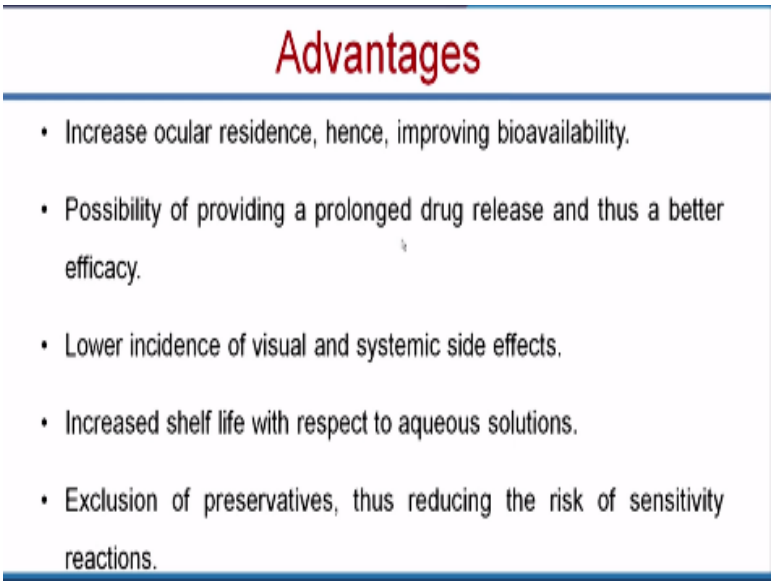

So here the advantages are increase ocular residence hence improving bio availability and it will increase the possibility o providing a prolonged drug release and thus a better efficacy, and also the lower incidence of visual and systemic side effects and increase shelf life with respect to aqueous solutions and exclusion of preservatives thus reducing the risk of sensitivity reactions.

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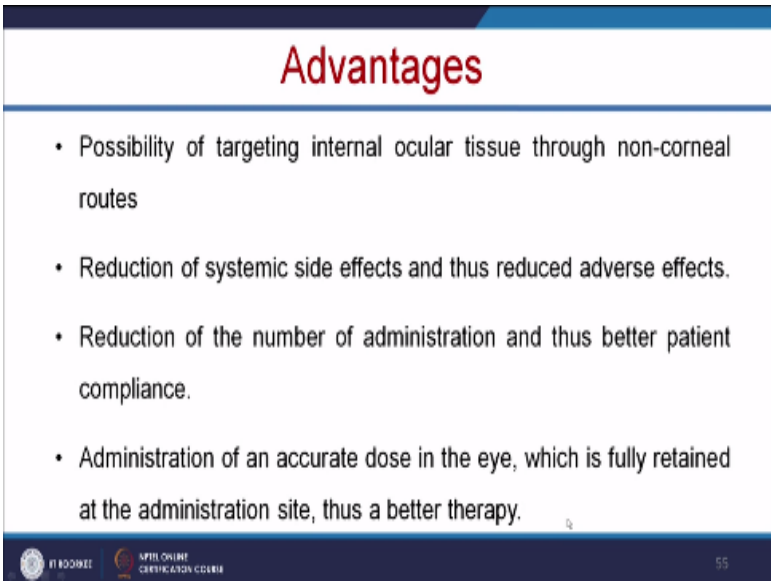

So other advantages are it will reduce the systemic side effects and thus reduced adverse effects and you can reduce the number of administration and thus better patient compliance and also the administration an accurate dose in the eye, which is fully retained at the administration site so that will improve the therapeutically efficiency.

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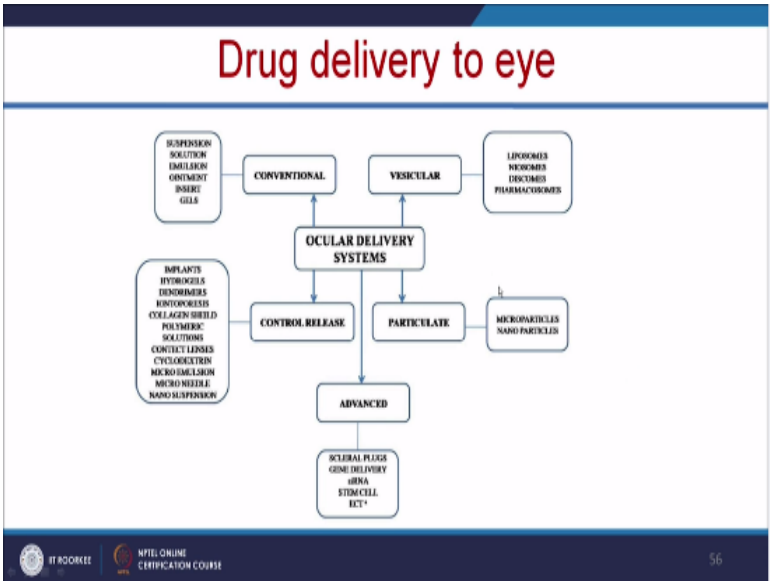

So we can deliver the drug to the eye using there are various carriers we can use the liposome okay we can also use the micro particles, nano particles, so depend on the drugs as well as depends on the diseases, sop according to the target we have choose the suitable carrier.

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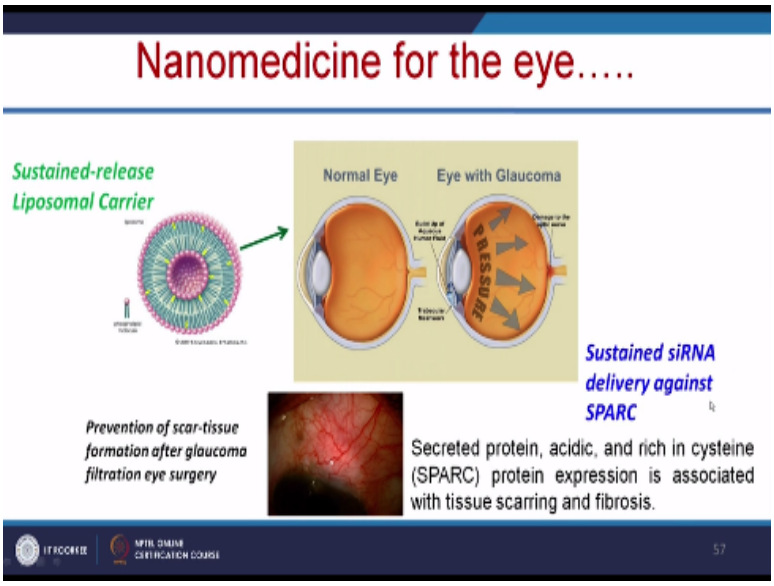

So let us see an example, so here you can see the normal eye and eye with the glaucoma okay, so we can liposomal carrier which can give drugs to this, again we can use the lipid carrier for preventing the scar tissue formation after the glaucoma filtration eye surgery. To prevent this formation of scar by using this sustained delivery against these SPARC. SPARC is secreted protein acidic and rich in cysteine okay. So we can reduce this SPARC protein expression is associated with tissue scaring and fibrosis.

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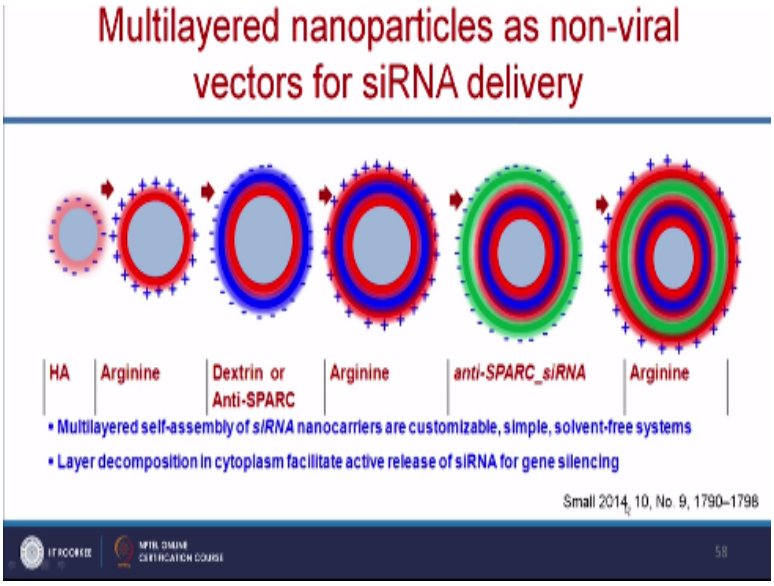

So we can use multilayered nanoparticles as non viral vectors for siRNA delivery, so we can have these kind of multilayered nanoparticles and which will be carrying the SPARC, so this multilayered self assembly of a siRNA nanocarriers are customizable and these are simple, solvent, free systems and this layer will be decomposition in cytoplasm and it will facilitate active release of siRNA for gene silencing okay. So this will be useful for preventing the SPARC after the gal co surgery.

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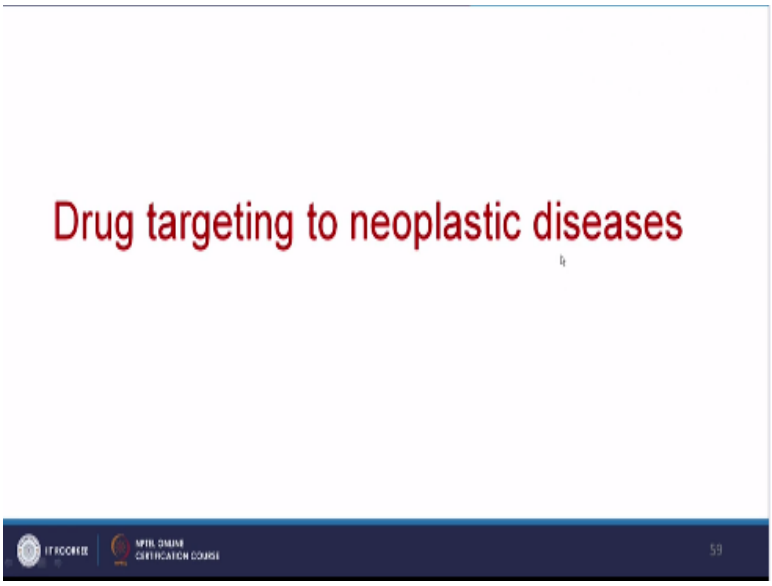

So let us see drug targeting to neoplastic diseases, neoplastic means cancer okay.

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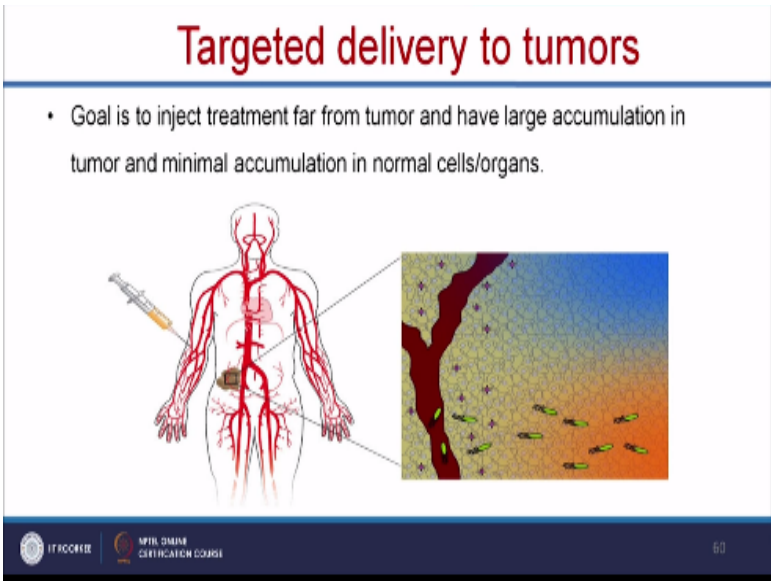

So here the goal is to inject treatment far from tumor and have large accumulation in tumor and minimal accumulation in normal cells and organs, so this target deliver tumors, I have already discussed in one of my previous lecture in detail but so briefly we will see here how we can use this.

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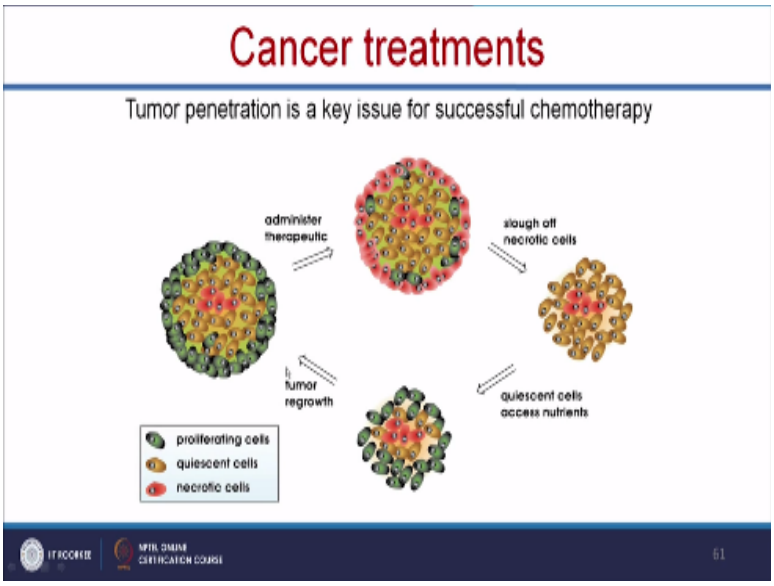

So here the most of the failure of the cancer treatment is the tumor penetration okay, so the tumor penetration is the key issue for the successful chemotherapy and most of the cases the drug cannot entered inside the location of tumor. So due to which what will happen? Tumor will re grow.

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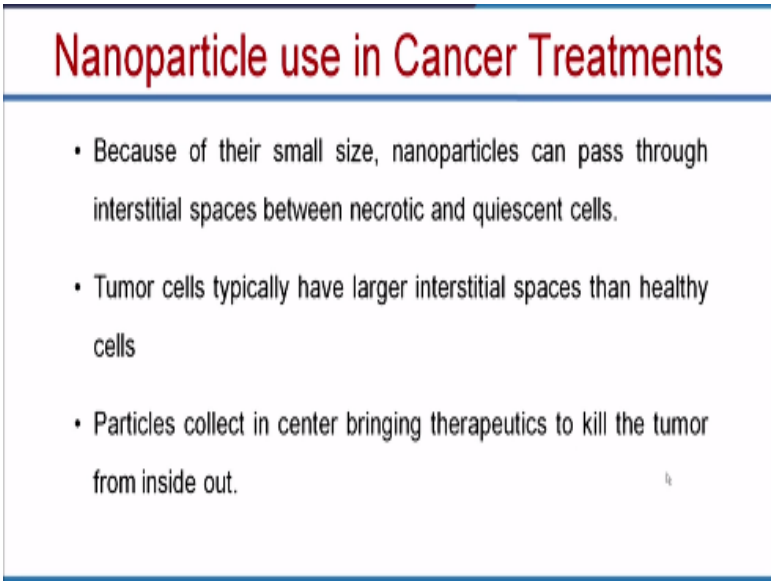

So to overcome the this we can use the nano particles, and this nano particles can pass through the interstitial space between necrotic acid and quiescent cells and this tumor cells typically have larger interstitial spaces than healthy cells and the particles collect in center bringing therapeutics to kill the tumor from inside out.

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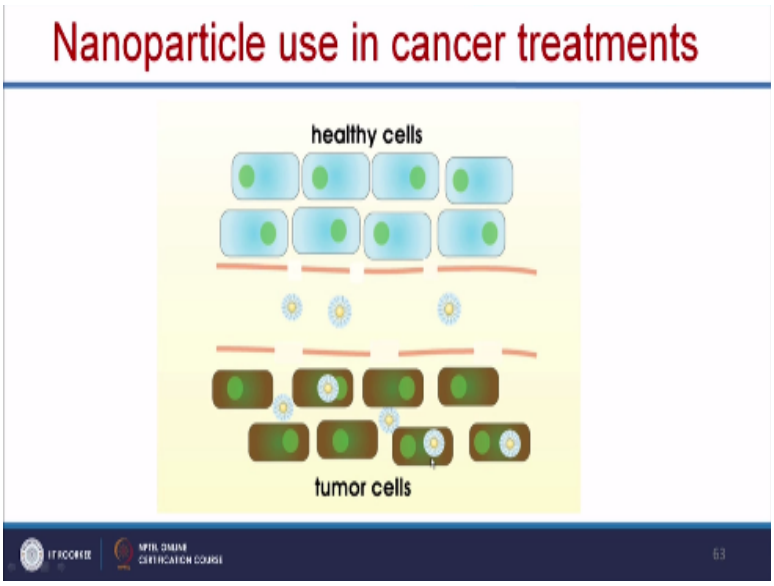

So you can see the nanoparticles can enter and only binding the tumor cells and can erratic the tumor cells.

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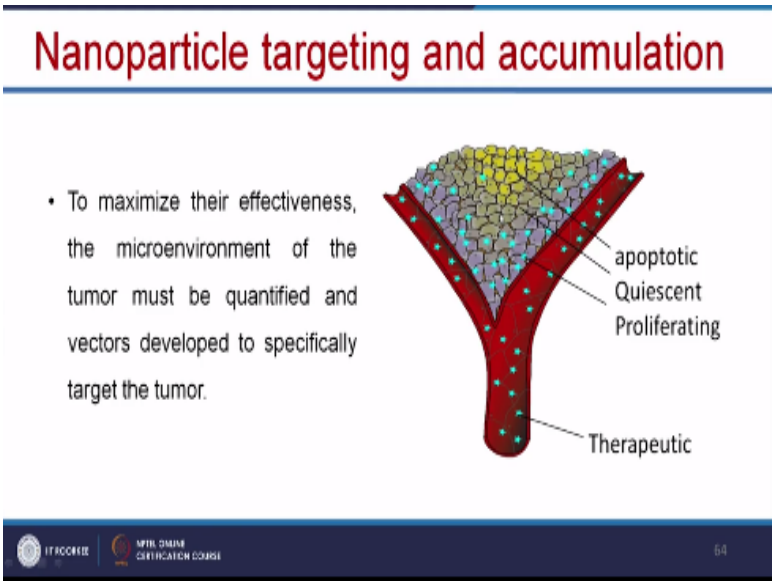

And these nanoparticles to maximize their effectiveness the microenvironment of the tumor must be qualified and vectors developed to specifically target the tumor. So it can reach the inner part of the tumor then it can completely erratic the tumor and it will prevent the re occurrence of tumor okay. In this lecture we have learn what nano pharmacology is and also we have learn what the various nano pharmacology targets are and how to target these drug to the particular organs okay. So I will end my lecture over here I thank you all for listening to this lecture and I will see you all in another interesting lecture.

For Further Details Contact
Coordinator, Educational Technology Cell
Indian Institute of Technology Roorkee
Roorkee – 247667
E Mail: etcell.iitrke@gmail.com. etcell@iitr.ernet.in
Website: www.iitr.ac.in/centers/ETC, www.nptel.ac.in

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