**Biomaterials for Bone Tissue Engineering Applications**
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**Indian Institute of Science Bangalore**
**Module 8**
**Lecture 39**

In this module I will be discussing that how to develop as some of that biomedical device prototype.

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Just to give an example I will discuss that that results from our own research that is the acetabular socket development of high sensitivity high density polythene HDPE – HA alumina based materials that is what we called as a hybrid composite. Why hybrid? Because it contains both the ceramic phase and polymer phase together.

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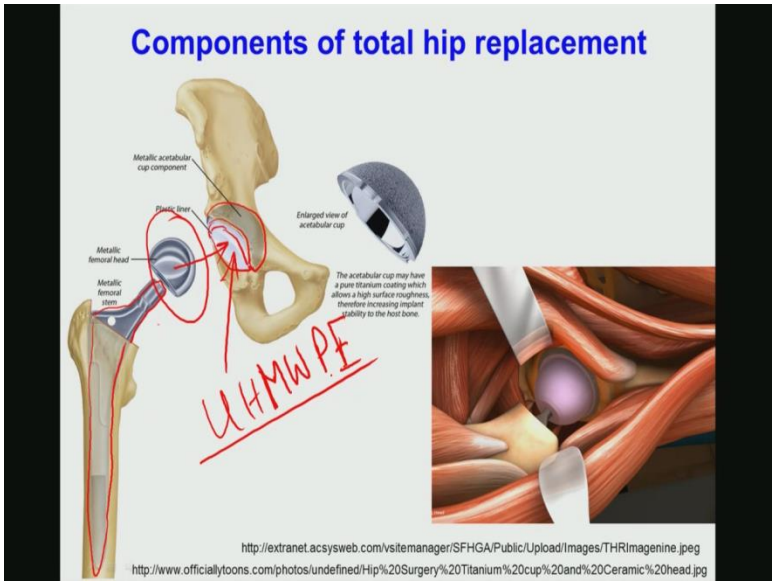


So, just to refresh your mind with this total hip replacement thing so, you have a metallic femoral head and you have a alkyl molecular polythene that acetabular liner. So, this alkyl molecular polythene that is a plastic liner this is acetabular component and then this metallic femoral head it will go straight and then fit it and this is a metallic femoral stem and this is the neck of the stem. This femoral head this stem goes into this hole cavity. Now what is most important for us or for the discussion in this module is that whether this clinically used ultra high molecular weight polyethylene that is highly cross linked ultra mold polyethylene can be replaced with one of the materials that we have investigated for last six to seven years and that is high density polythene HDPE-HA alumina.

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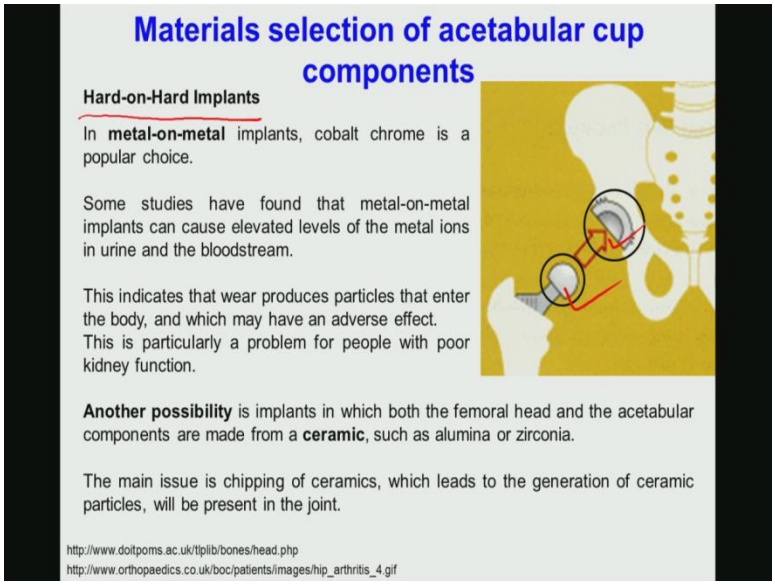


So, any of this so, some more details on materials selection for acetabular cup or acetabular socket component, now in this module I will be interchangeably using that cup and socket so although they are all synonyms. So, there is one class of material THR implants essentially hard and hard implants, hard and hard means you you can use both ceramic as acetabular socket and ceramic as the femoral ball head together. So, both this guy and this guy can be made of ceramic or it can be made up of a metal. For example, metal and metal like cobalt chrome is a popular choice.

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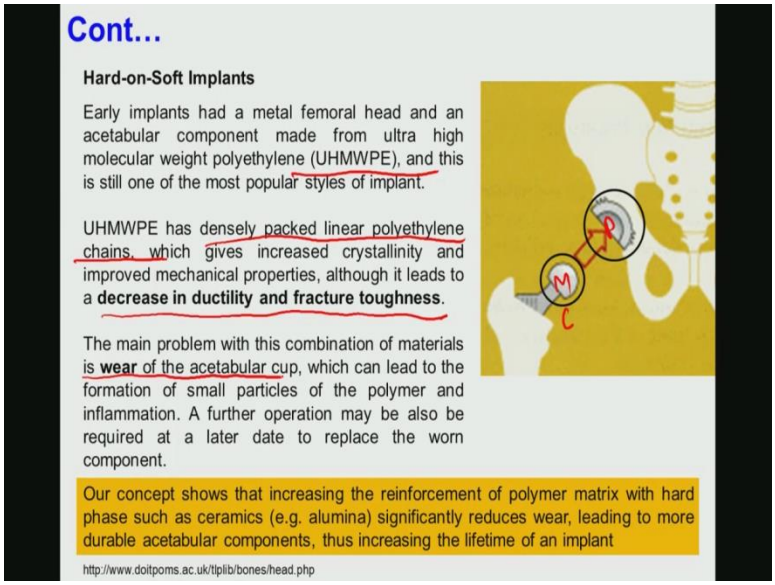


So, the second one is that hard on soft implants. What is the meaning of hard on soft? This guy can be metal or ceramic and this can be polymer that is acetabular socket can be polymer. And here ultrahigh molecular weight polyethylene can be used but ultrahigh molecular weight polyethylene is a highly has densely packed linear polyethylene chains which keeps increased crystallinity as well as improved mechanical properties. But however ultra molecular polyethylene does not have a large elongation to failure and also has a poor fracture toughness and as a and also it has a poor poor wire resistance.

As a result ultra molecular polyethylene is acceptable to wear and therefore that leads to wear debris particle particle generation in the In-vivo. And this wear debris particle is depending on their size and shape they can cause certain inflammatory reaction in the In-vivo conditions. That is number one, number two is that if the wire is very expensive then patient has to undergo the replacement surgery or the revision surgery that means the patient has to go to hospital and go to that operation theatre again.

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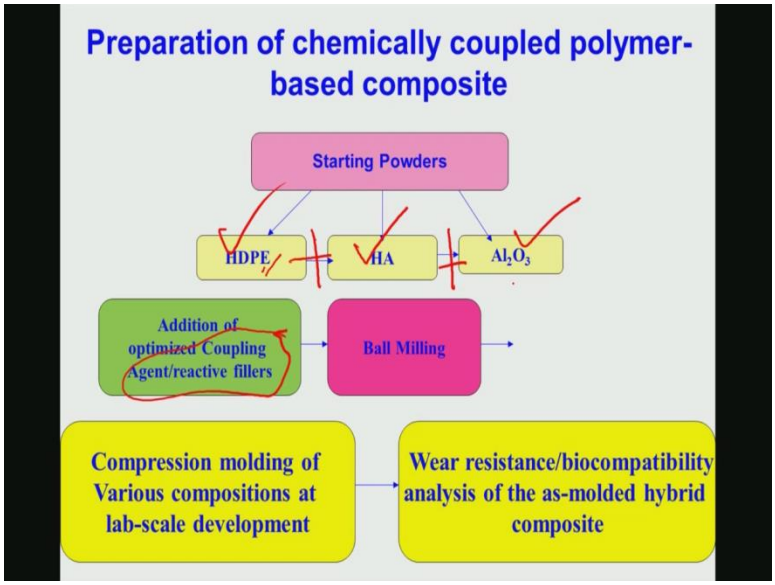


So, there are 3 starting powders one is HDPE, HA, Al2O3 and then you do ball milling. Now as you see that HDPE has a very simple polymeric chain carbon, hydrogen, HA has a different composition organic inorganic composition, alumina is different inorganic composition. If you do not couple these things by chemical means like using a coupling agent or reactive fillers you cannot do much in terms of the achieving better and mechanical properties. So, coupling agent essentially this coupling can be tightened coupling agent so on this tight is, coupling agent essentially help in establishing certain chemical bondage of that inorganic component with that of the HDPE.

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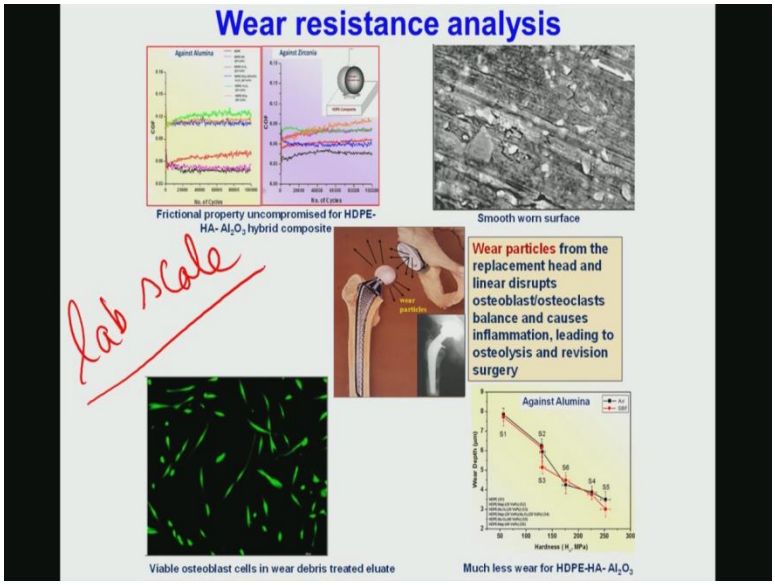


So, in time this kind of prototype development for this research is there, first one has to do that lab scale experiment. Lab scale experiment means one can start with that compression molding of this materials and for example, I mean you can do injection molding, you can do compression molding this time polymer ceramic composites. So, one can do lab scale experiments.

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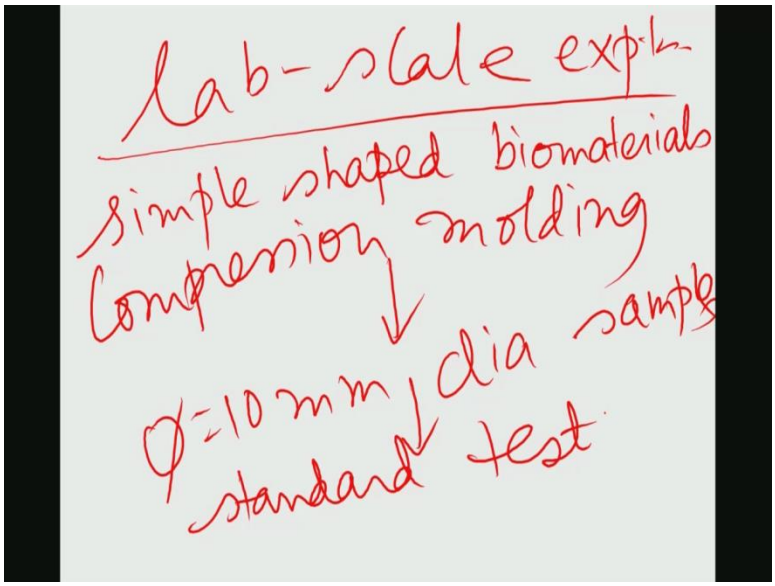


So, lab scale experiments essentially start with simple shaped biomaterials. Now, simple shaped biomaterials means you can do compression molding and with a very simply steak mold shape

and all. So, compression molding and then it can give you let's say 5 equal to 10mm diameter samples and you can do standard tests.

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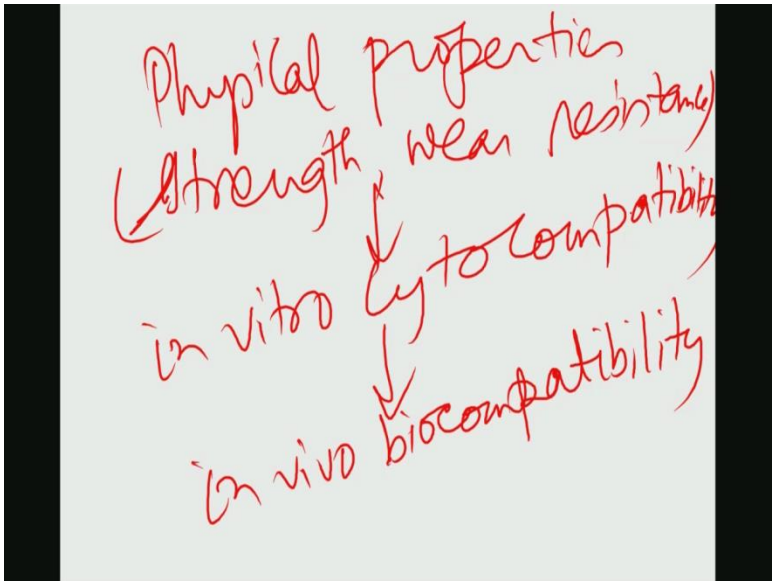


Now, this standard test can be either physical property measurements like hardness, strength and so on of these materials, strength, wear resistance properties. Now, the second thing you can do some In-vitro In-vitro cyto compatibility property and followed by one can conduct that In-vivo biocompatibility of selected samples, ok?

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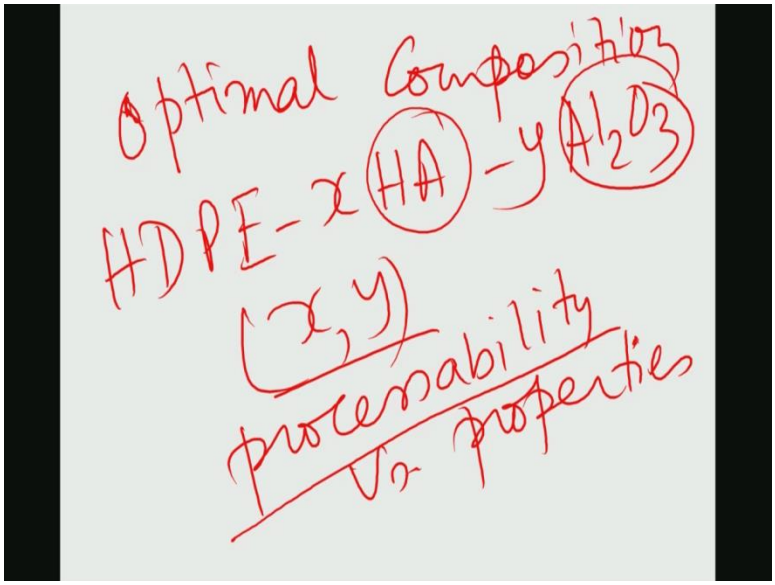

So, this so, this so, what one has to do is that, first one has to screen what is that optimal composition. Now, let's talk about little bit of the material science here. Let's say you have HDPE as a matrix and you have X% HA and Y% alumina. So, first you have to optimize that percentage of the X and Y, now here you have to consider that what is the processibility or ease of processing versus properties. Now, HDPE although it has a low strength but it has some beneficial properties like large elongation to failure. High density Hydroxyapatite alumina this is ceramic phase inorganic phase the moment you add this to HDPE then it will decrease this elongation to failure instead it will increase both elastic modulus and hardness of this materials and strength of the materials.

Having said this more and more HA more Al2O3 is present in the HDPE matrix it will have an opposing effect on the processibility or moldability. Because by adding this HA and by adding this alumina your viscosity would increase, of that viscosity of that HDPE melt would increase. So, higher the viscosity more is to mold this kind of material or more difficult is to give certain shape to these materials. So, you have to critically consider the processibility of this material v/s what are the properties of this materials.

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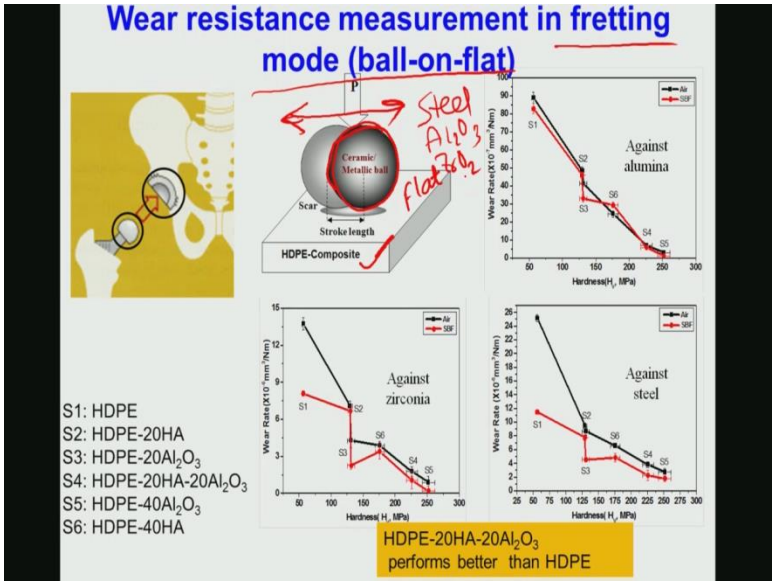


So, as I said that one of the major motivation to develop HDPE HA Alumina is to enhance that wear resistance properties of this material and this typically wear resistance is investigated using that fretting mode. Fretting essentially means that is a ball-on-flat type of configuration. So, this

ball is made to slide in a reciprocatory motion against this flat material and this relative displacement amplitude is of the order of 100 to 200 micron. That is called stroke length. Now, when this kind of reciprocatory motion is there, when this kind of stroke length is there then what will happen is that that these at these regions interruption region there is wear debris particles will be generated or this HDPE composite will be will be will experience that wear loss and so on. So, one can measure that wear rate.

Now, two aspects we have studied, we have changed the you have changed the counter body we have used 3 different counter body. One is steel, one is alumina and one is zirconia. The selection of these counter bodies can be rationalized from the fact that, stainless steel based material is widely used this one of the femoral head. Alumina, zirconia these are other potential femoral head materials.

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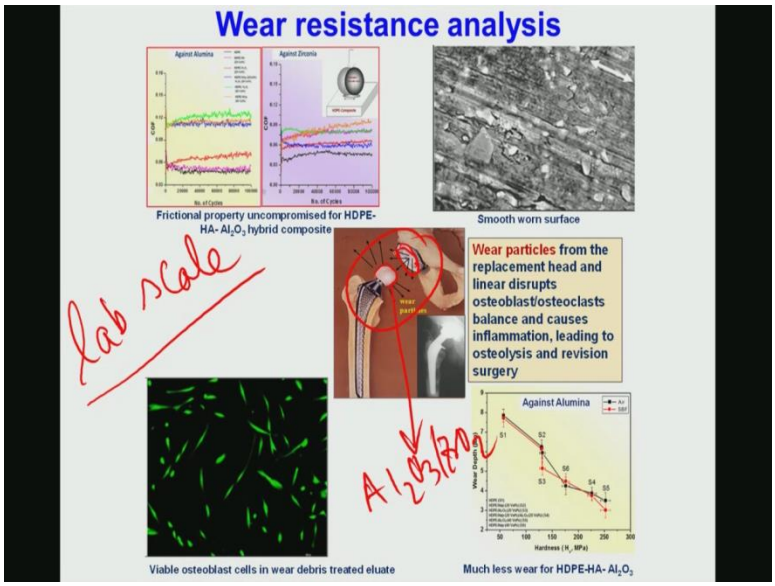


So, essentially we are trying to simulate what is the exact contact conditions that essentially present here. For example, so, I am saying that femoral ball head can be either alumina or zirconia, and then acetabular socket we are saying that instead of ultrahigh molecular weight polyethylene this part we are trying to replace by HDPE HA alumina. So, therefore we need to study that in a simplistic more simplistic scenario in the lab scale experiment. Hence we have to conduct that fretting study between the femoral head and acetabular socket, ok?

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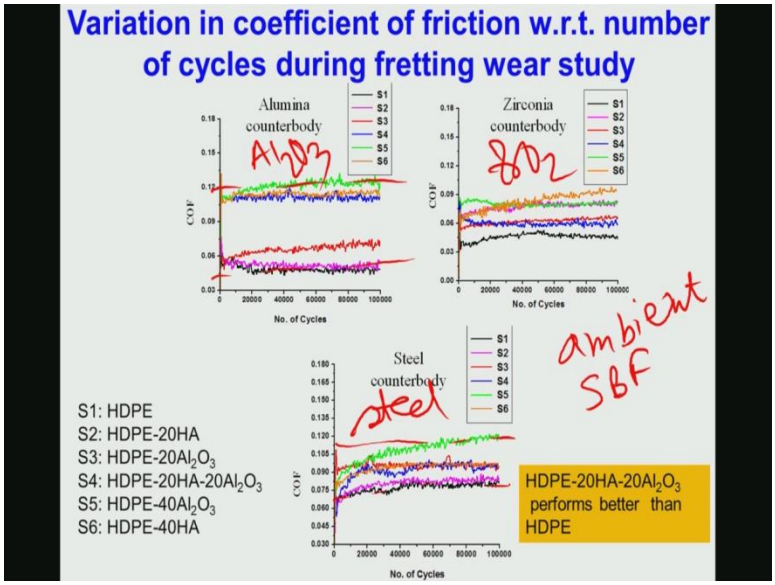


And then you can measure that what is the friction hollows and this fretting experiments are can be conducted and their ambient conditions. And on that SBF conditions, SBF stands for Stimulated Body Fluid. So, under these two different conditions, when you use this alumina whether when you use this zirconia and when you use the steel, in all these cases what you see that coefficient of friction typically varies in the close window of 0.7, 0.07 to 0.12. The same is true for 0.11 to 0.7. So, depending on the steel, zirconia and alumina, typically the coefficient studies that coefficient of friction is less than 0.1. So, lower the coefficient of friction better it is.

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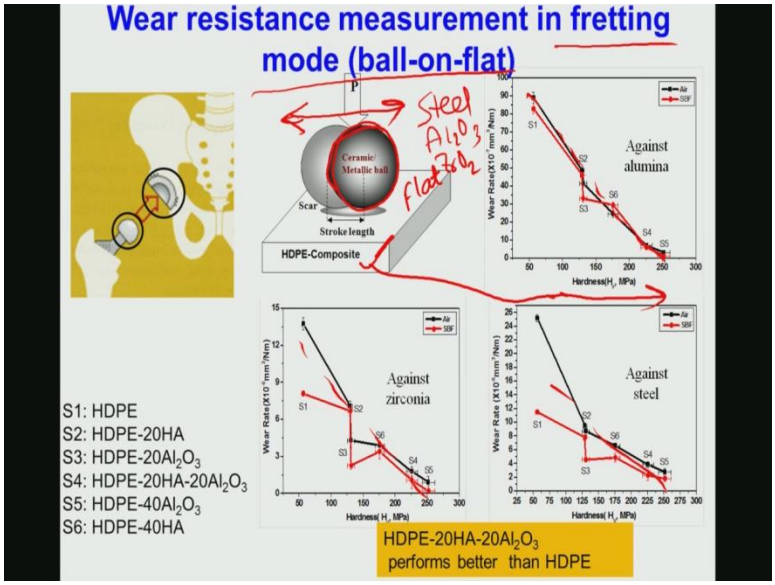


So, in terms of the wear resistance what you notice here as you increase the hardness of the flat material let that is the HDPE HA Al2O3, then wear rate sequence decreases wear rate sequence decreases or systematically decreases. What it means by adding HA Al2O3 to HDPE you can increase the hardness of the material but you also increase that wear resistance of the material without compromising much on the frictional properties.

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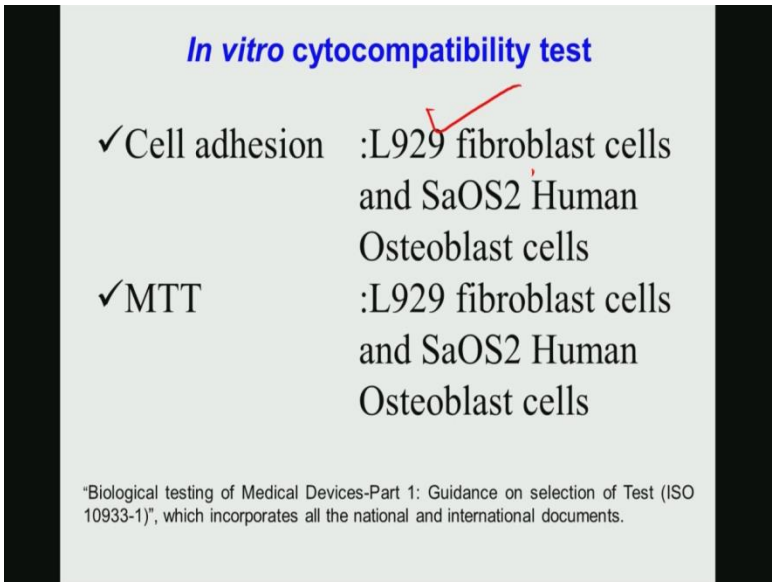

Some of the In-vitro results so, we have used L929 fibroblast then SaOS2 cell lines, we have done MTT and then we have followed that ISO109931 that is the typical guidelines.

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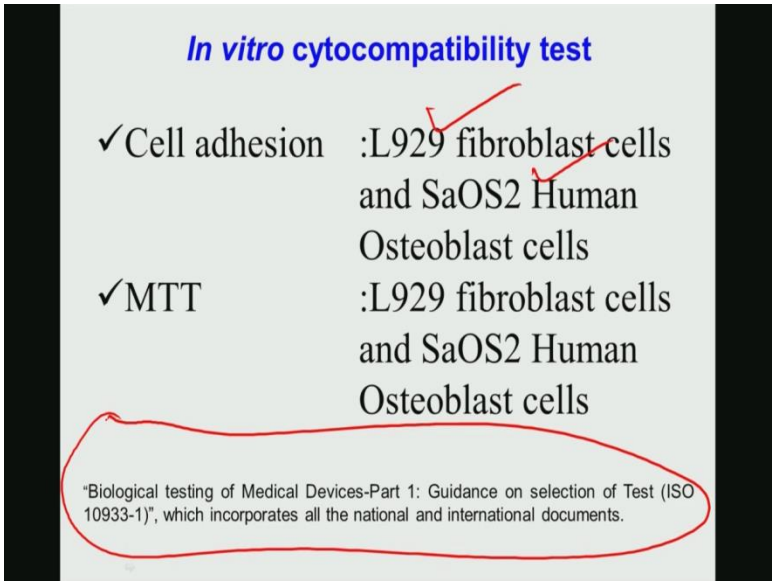


So, this is that ACM scanning electron microscope image of the SaOS2 cells which is essentially shows that typical flat morphology which is exactly that is the Osteoblast like cells that they will exhibit that is the typical morphology. Now, in terms of number of days in culture in 3 days, 5 days and 7 days, you see that main optical density also increases essentially that more and more number of mitochondrially viable cells increase with time in culture.

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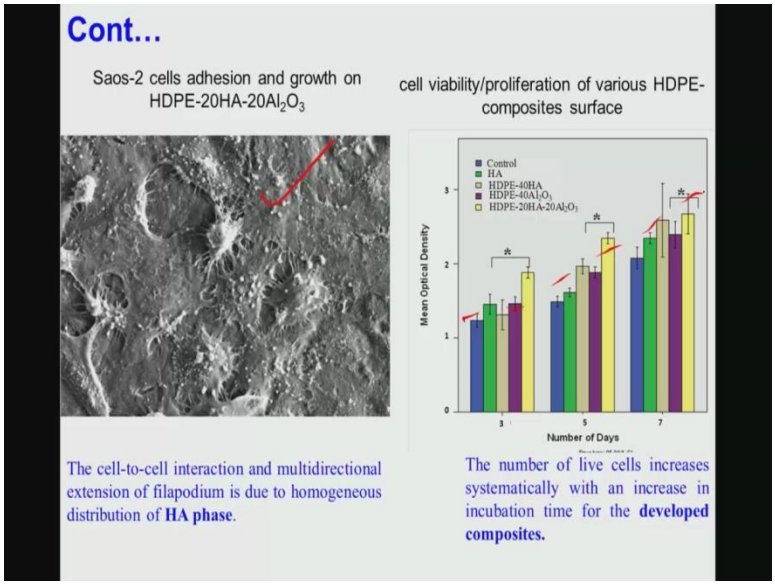


In terms of the In-vivo implantation we have done two type of experiments for two different time period both in rabbit. So, in one case we have used femoral bone defect model as I have also mentioned in some of my earlier lecture. In another module and another case we have used large segmental defect. Large segmental defect means some part of the femur is cut and then you to implant the similar sized implant to feel that large segmental defect. So, instead of making hole, you can simply cut the femoral part, femur part and then put the implant there.

There is something in a biomaterials literature there is some other term is there that is called critical size defect. So, it is also one type of the segmental defect. The term critical size defect essentially means, the defects length is around 2 to 3 times of the diameter of the anatomical location or anatomical part where you are placing. So, to substantiate the statement what I am saying is that, for example, if you are putting the critical size defect in the femoral or femur part of an animal, so, you know that what is the femur diameter that the length of the segmental defect should be 2 to 3 times than that of the femur diameter then only you can call critical size defect.

Now, in all these cases one has to see that how this critical size defect is healed over several times frame or several time span and so, therefore in the large segmental defect we have done a (())(14:52) to medical science where we have done this experiment up to 26 weeks. And the femoral bone defect model we have done this experiments all this femoral bone defect model we

have done this experiment that City Science Institute of Medical Science and Technology and that is for 12 weeks. And 12 weeks typically people call it as a short term implantation experiments. Then after that you see the cystology images and son on and this is your SEM image. In both the cases you see that there is a new bone generation and you can say that is high version remodeling and this is clearly shown at the interface zone and this is your cortical bone and it is the host bone here also it is a cortical bone and then another part is here normal implant.

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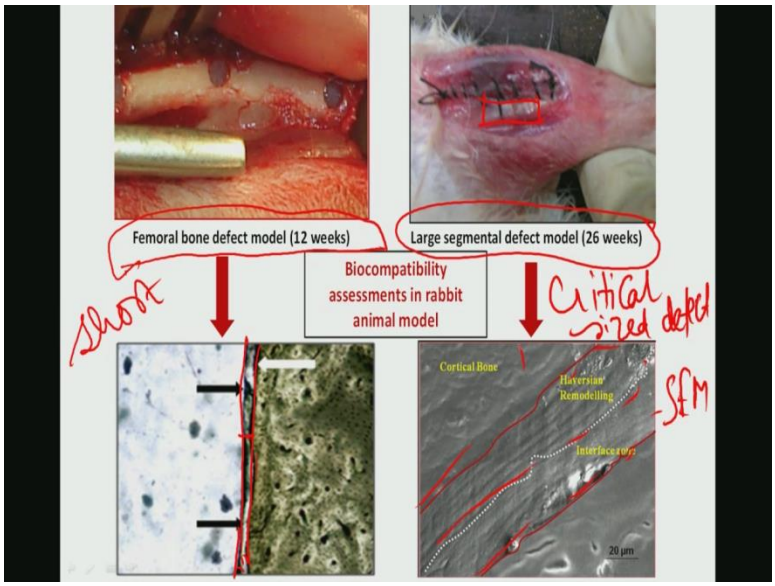


This is the case of this implantation in the segmental defect model here you can see that it is placed in this sutures and so on. And this is that how this transplant looks like in the extra radiograph in the rabbit model.

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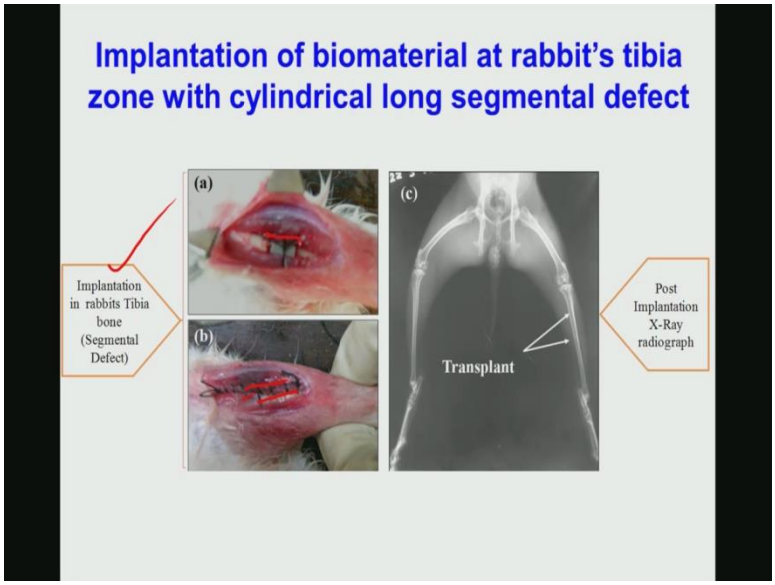


This is more evidence of the new neo bone formation of the histology slide that you have this trabeculae bone here that's very spongy, you have the neobone on this material and you have some osteocytes activity because osteocytes they appear with different morphology and which can be distinguished from osteoblasts as I have said before. Osteo besides are more star shaped morphology.

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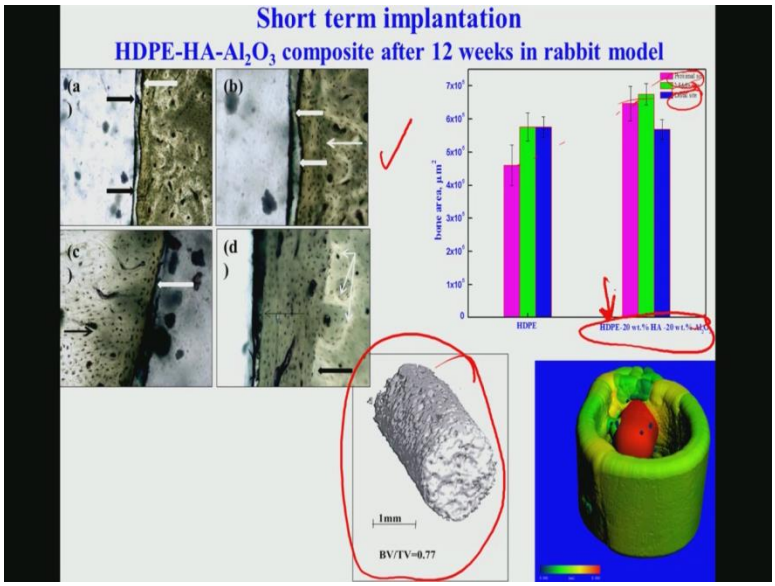

Now, in the short term implantation we have done some a microcity analysis also and it show that bone volume to total volume and then you have done also we have done also this histology images and see that what is the typical bone area of this materials and what is that bone area in the distal side in the middle side and a proximal side. So, normally what you see that with a with respect to HDPE with a HDPE HA Al2O3 composite not only your osseointegration is uncompromised but also quantitatively bone contact area increases that means that this material promotes more and more bone regeneration around this implant.

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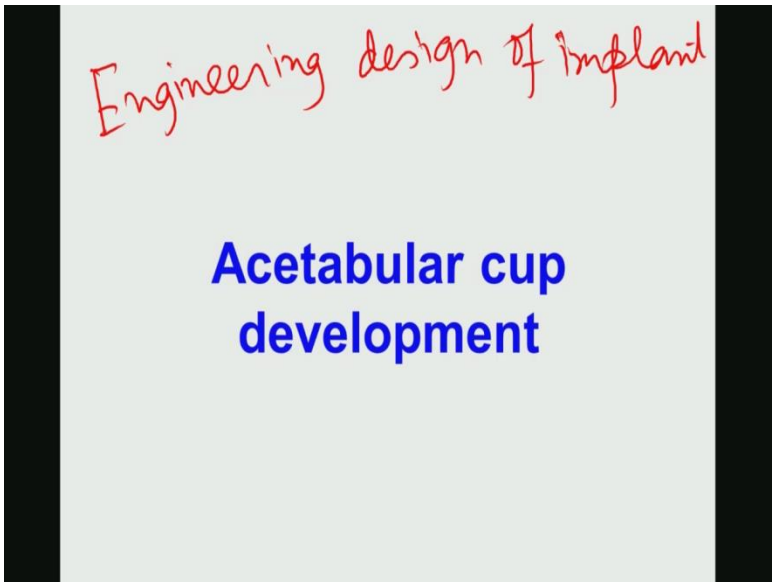


Now, once you establish all these lab or once you complete all these lab scale experiments, next stage is to acetabular socket acetabular cup development or any device development. So, first and first thing that one has to do is to get an engineering design file of the device or implant. Now, engineering design of the implant can be you can take a commonly used device diameter which is used in a given patient population or you can take a patient's specific dimensions like you take the CT data from the patient itself then you convert it into the engineering design file and then engineering design based on the engineering design file either you can give it as an input file with the 3D printer or any rapid proto typing machine so that you can get a neon net shaped device or based on the engineering design file you now fabricate your experimental processing or manufacturing facility to get this kind of device. Let's say acetabular cup development ok?

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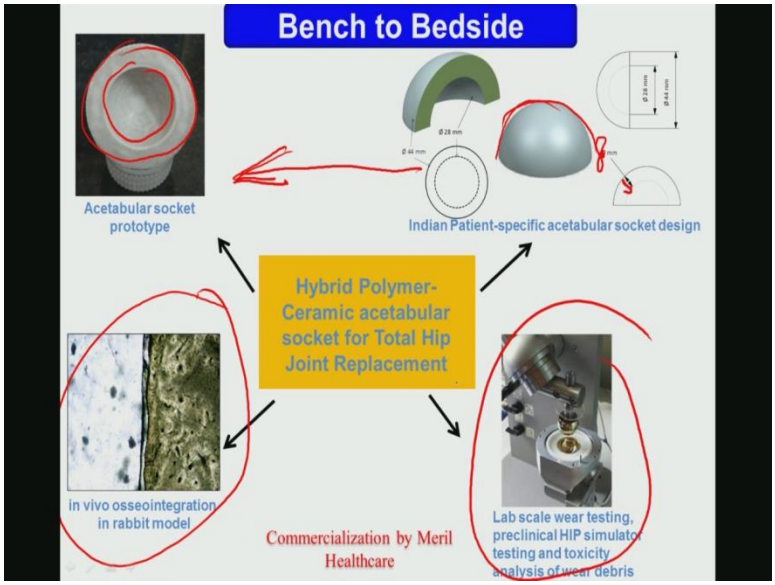


Now, this is the Indian patient's specific case what you see that this is your wall thickness is 8 mili meter here and this is your outer diameter is 44 mili meter inner diameter is 28 mili meter so, rest of the thing is your 8 mili meter. Now, this is how that acetabular socket they look like this acetabular socket and this is the different aspect of first is the engineering design, then you do compression molding in a large scale set up, then this is essentially based on the In-vivo Osseo integration and then you can do this ultimate other things is that that this total hip joint total Hip simulated experiments.

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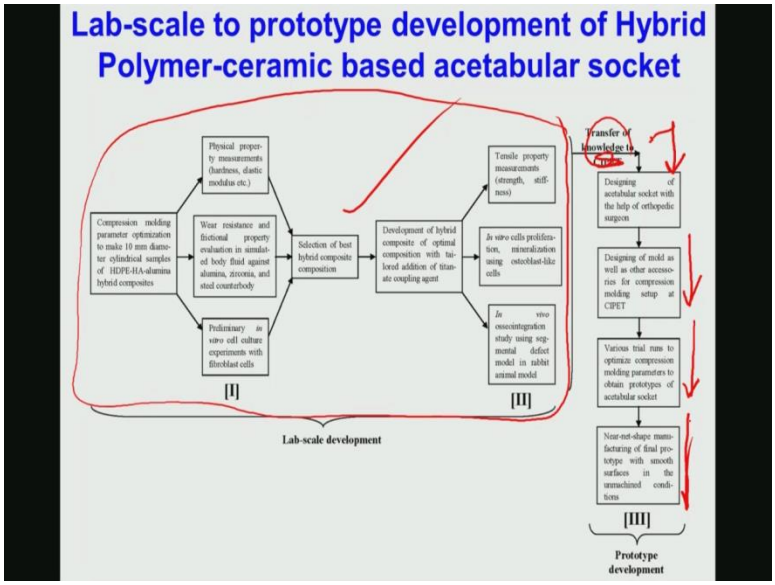


Now, just to give a snap shot of the things that this first whatever I have shown in this particular slide is that first is the lab scale development. Now lab scale development I have already described. Now, next type is that prototype development and in prototype development first thing is that designing of the acetabular socket, then designing of the mold and various trial rounds to get this compression molding and then you can prove this neon net shaped manufacturing.

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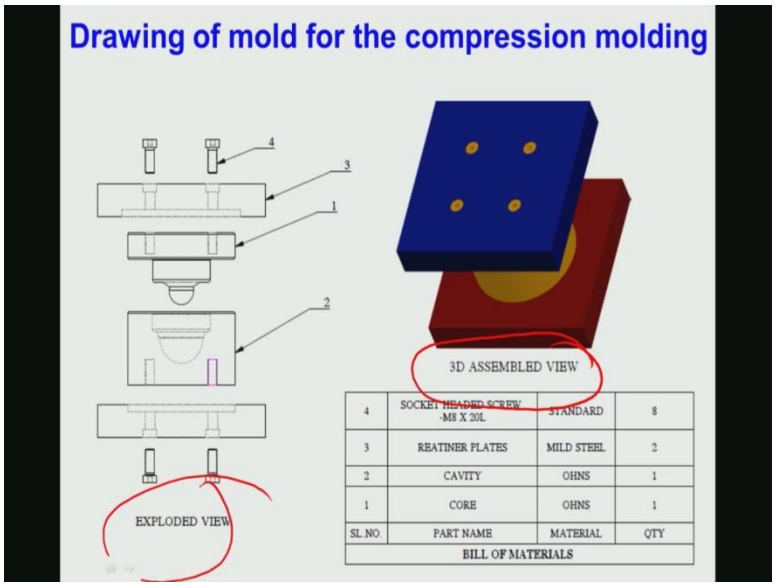

So, this is the engineering design file, based on that you can do that compression mold geometry fabricate this compression mold with a specific geometry like this is a 3D assembled view and this is the exploded view. And this is the different retainer plates cavity and cores and this is the mild steel and then other material that we have been used.

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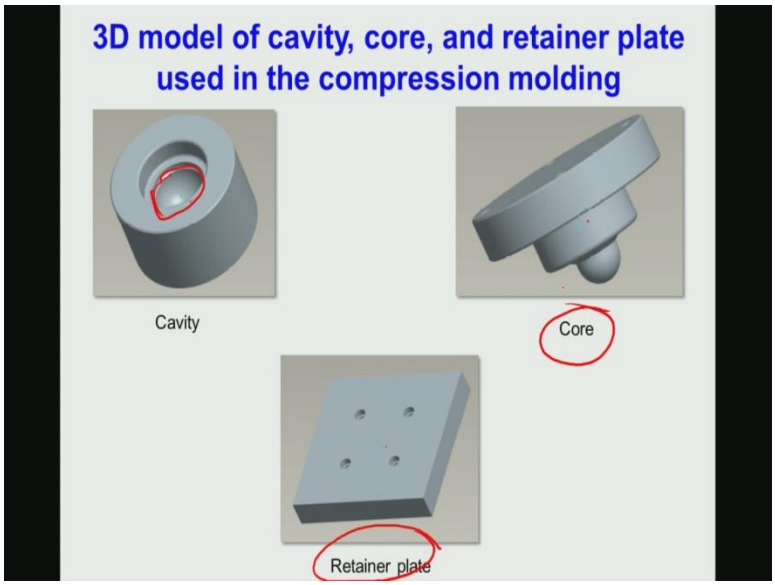


So, this is the cavity. So, the cavity should reflect that what would be the ultimate shape of the femoral a.. acetabular socket material that you want to develop. This is a core part and this is retainer plate. These core part and retainer plate is that part of this inter compression molding assembly that we are using and this is the total compression molding assembly as you can see.

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So, this part of the work can be was carried out in Central Institute of Plastic Engineering Technology, Chennai and this is through a heating coil arrangement. You can locally heat this entire assembly. But this heating requirement is fairly minimal unlike ceramics, so, here if you heat it at close to 200 or below 200 degree Celsius and it contain HDP that should be fine.

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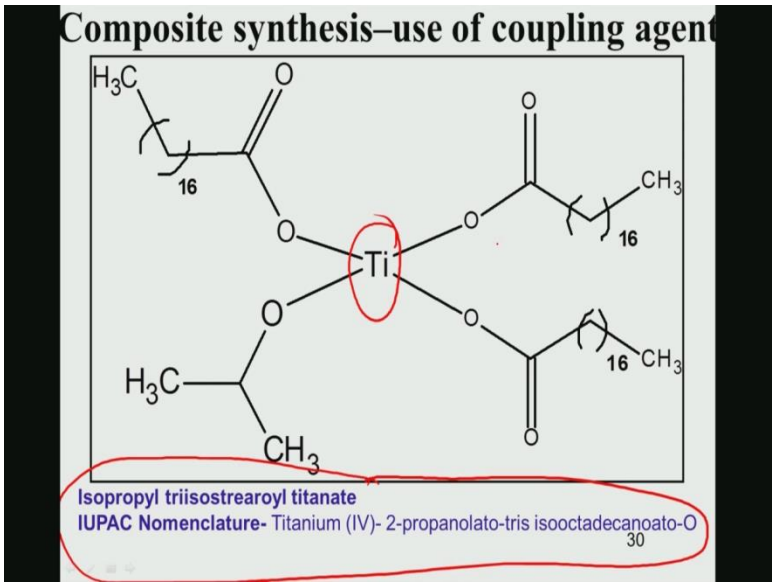


Now, earlier I mentioned that coupling agent is to be used and one of the coupling agent that we have used it is titanate based coupling agent with these particular formulations. What you see is a

titanium in the central and then all this chemical compositions is very characteristic of this particular coupling agent.

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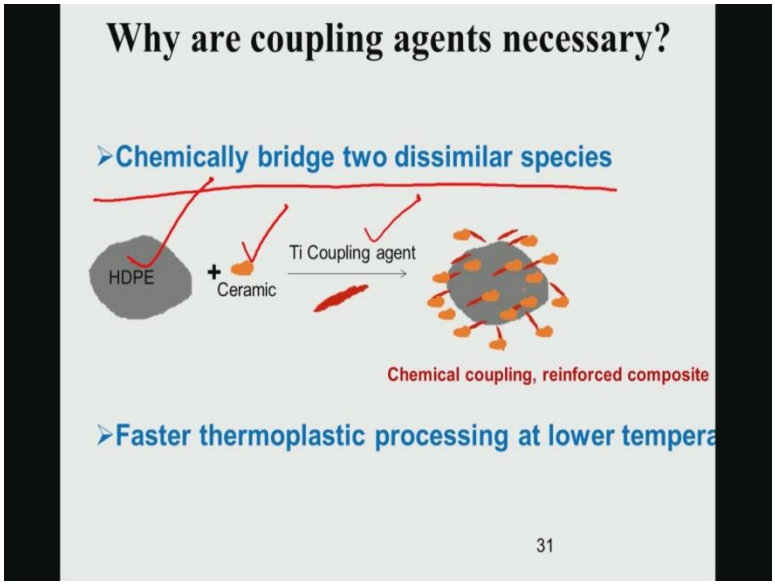


So, as I said that by coupling agent is necessary now this chemically bridged two dissimilar species that means to which are chemistry wise different. And so, here is a titanium coupling agent, you have HDPE and you have ceramic and you get chemical coupling that means reinforced composite. And therefore this first thermoplastic processing can be accomplished.

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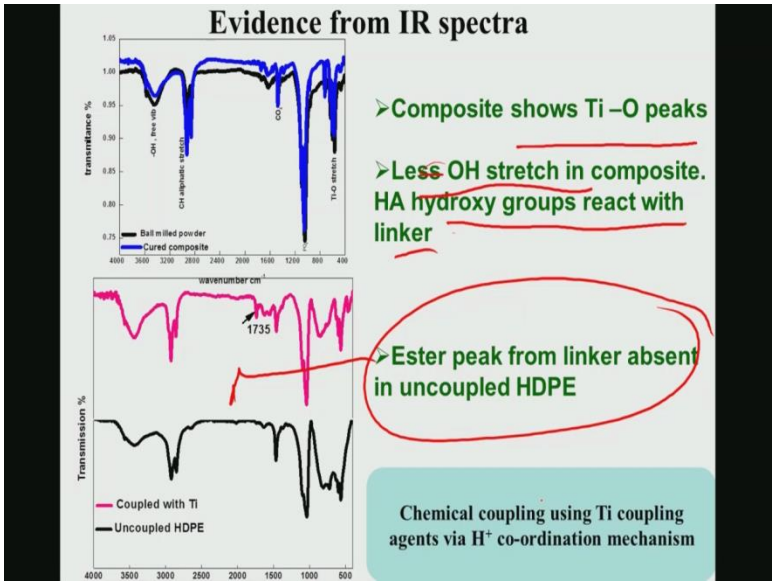

Now, this once you do this powder mixing and ball milling this coupling agent this HDPE what it shows that it shows some titanium and oxygen peaks less this OH stretch that means essentially shows that it is Hydroxyapatite hydroxyl groups react with that linker and also one can notice here that it's a peak here and this is for which is absent in the uncoupled HDP.

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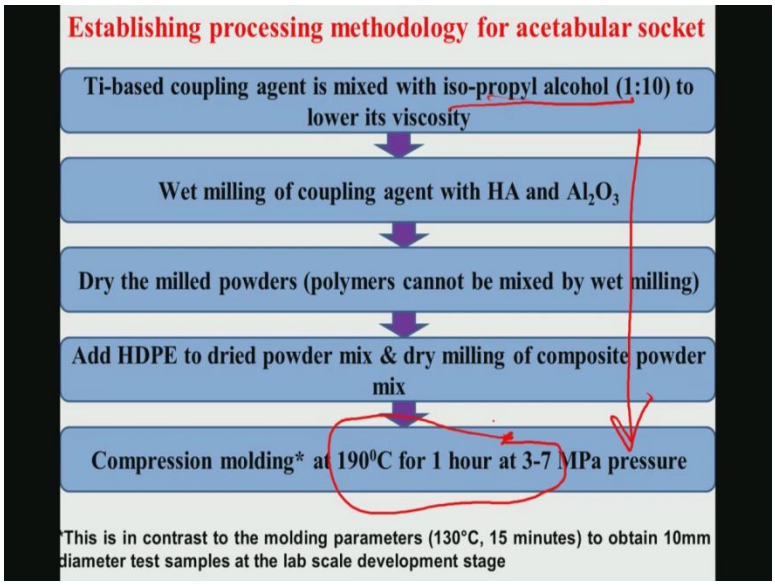


Now, as per the processing is concerned we one can use certain 2% or 3% of the coupling agent and you can do isopropyl alcohol as a medium for this who makes this coupling agent with these powder mix then after this you can do this compression molding of this large acetabular socket type of device at 190 degree Celsius for 1 hour at a very fairly moderate pressure 3 to 7 megapascal.

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And this is how this compression mold socket that looks like and this is your as fabricated neon net shaped and so you don't need to do much machining or you don't need to do any machining to get the final shaped and this is kind of really elastration of the neon net shaped of fabrication of the acetabular socket.

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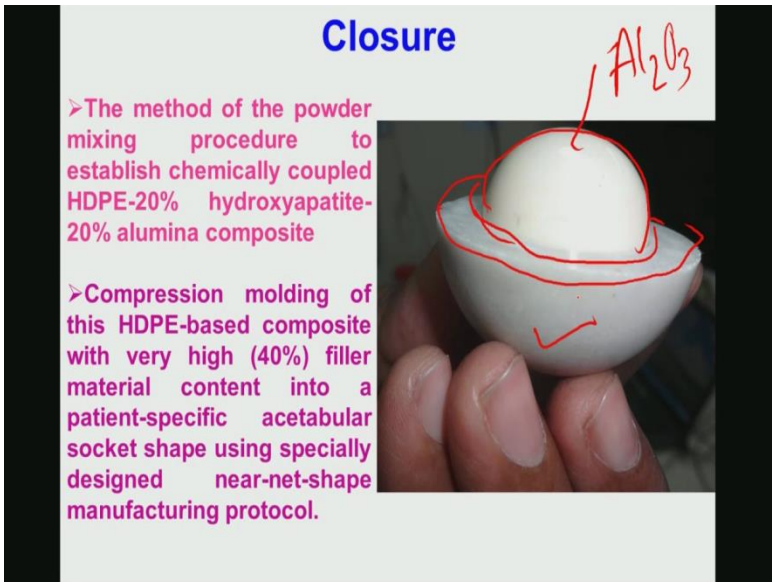


Now, this is what can be seen this is your alumina femoral head, somebody is holding this alumina femoral head with this acetabular socket just to show that how geometrical conformity

can be established in this process so that alumina femoral head exactly going inside and fitting into the acetabular socket. And in the process we have also established that what is the fabrication route, how to fabricate this large this one, although I have not shown that when we did this microcompetent chromography of the ultra (())(23.09) HDPE based socket, we did notice that uniform distribution Al2O3 and also it is a crack free and pore free composite. So this process also can also is capable to produce some of the structurally robust device component.

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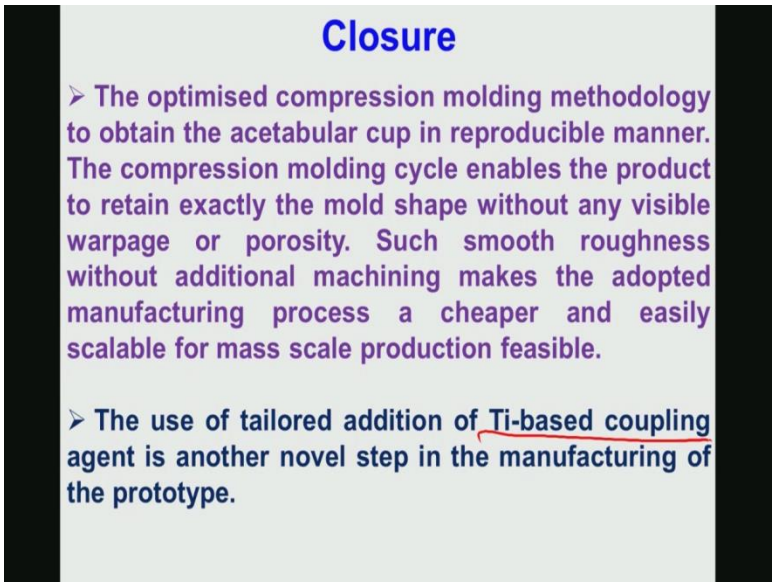


So, this is the some other note that I would like to mention that we can use the titanium based coupling agent like titanate and so on. And this material has a surface toughness of less than 1 micron which is clinically acceptable like 0.5 to 0.6 micron. Thank you.