Tissue Engineering

Prof. Vignesh Muthuvijayan
Department of Biotechnology
Indian Institute of Technology, Madras

Lecture - 09
Bioceramics

Let us start with today’s lecture. Today, we will be talking about Bioceramics. We have primarily talked about polymers till now, because those are one of the most well-studied class of materials for Tissue Engineering applications, especially for scaffolds. Here, we will be talking about bioceramics today.

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Bioceramics

- Large class of inorganic non-metallic materials
- Used in repairing and replacing skeletal and hard tissues such as hip-joints, teeth, and bone
  - Antimicrobial activity
  - Resistance to pH change, acid and base solutions, and high temperatures
- Show better tissue responses than polymers and metals
  - Don’t release any compounds into the human body
    - Do not generate a foreign body response
    - Biocompatible to cells
  - Can bind directly with bone

This is a large class of inorganic non-metallic materials that are used in repairing and replacing skeletal and hard tissues such as hip joints, teeth, bone, etcetera. They can have antimicrobial activity, and they are resistance to pH change, acid-base solutions, and high temperatures. They show better tissue responses than polymers and metals. Here, I am talking about polymers that are synthetic and not present in your body.

In the case of ceramics, there are many ceramics which actually interact well with their body and integrate very nicely. They do not release any compounds into the human body, which will cause foreign body responses. In general, they are biocompatible to cells and can bind directly to the bone. So, they fuse to bone to form one entity.

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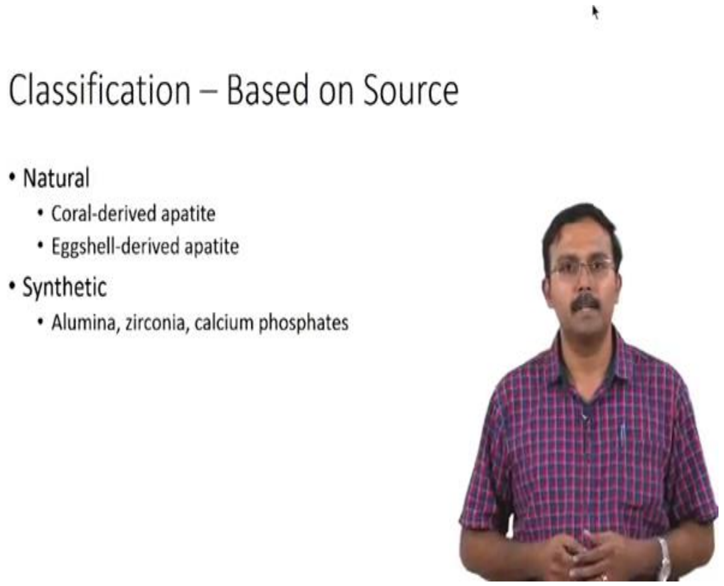

Classification – Based on Source

- Natural
  - Coral-derived apatite
  - Eggshell-derived apatite
- Synthetic
  - Alumina, zirconia, calcium phosphates

They can be classified based on the source as natural and synthetic. Examples of natural would be coral-derived apatites and eggshell-derived apatites. Coral-derived apatites have been studied for a long time; they are even FDA approved for use as bone substitutes. Eggshell-derived apatite is something, which people are interested in, and there has been some momentum towards understanding whether these can be used for bone tissue engineering and drug delivery applications. Synthetic ceramics include alumina, zirconia, and other calcium phosphates from different sources that have been used for bone tissue engineering applications.

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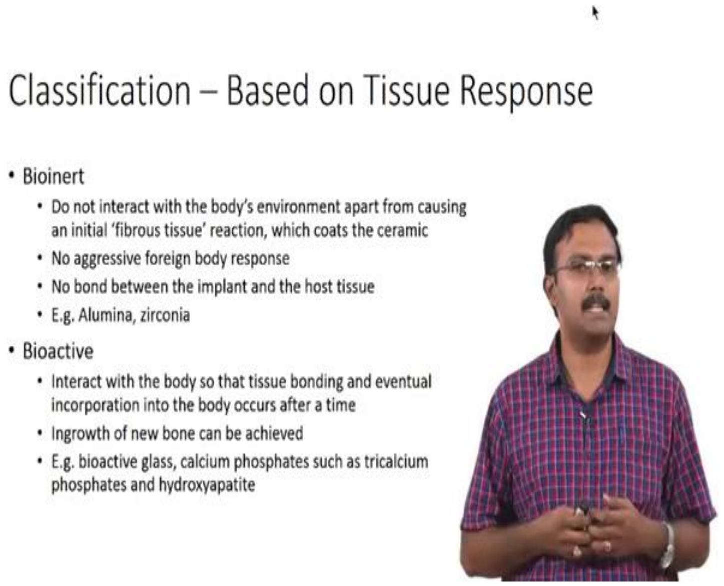

Classification – Based on Tissue Response

- Bioinert
  - Do not interact with the body's environment apart from causing an initial 'fibrous tissue' reaction, which coats the ceramic
  - No aggressive foreign body response
  - No bond between the implant and the host tissue
  - E.g. Alumina, zirconia
- Bioactive
  - Interact with the body so that tissue bonding and eventual incorporation into the body occurs after a time
  - Ingrowth of new bone can be achieved
  - E.g. bioactive glass, calcium phosphates such as tricalcium phosphates and hydroxyapatite

Based on tissue response, you can classify ceramics as bioinert or bioactive. Bioinert is a ceramic, which just not interact with the body's environment, apart from causing the initial formation of fibrous tissue. This fibrous tissue will coat the ceramic, and further, there is no other interaction. There is no aggressive foreign body response to these bioinert materials. At the same time, they do not bond with the bone tissue. The examples of bioinert ceramics are alumina and zirconia.

Bioactive ceramics can bond between the host tissue and the implants. Bioactive ceramics interact with the body. Hence, the tissue binds with the ceramic, and there is eventual incorporation of the implant into the body itself over a period of time. In growth of bone can be achieved for these bioactive ceramics. The examples would be bioactive glasses that are non-resorbable, and you also have resorbable bioactive ceramics like calcium phosphates such as tricalcium phosphate and hydroxyapatite.

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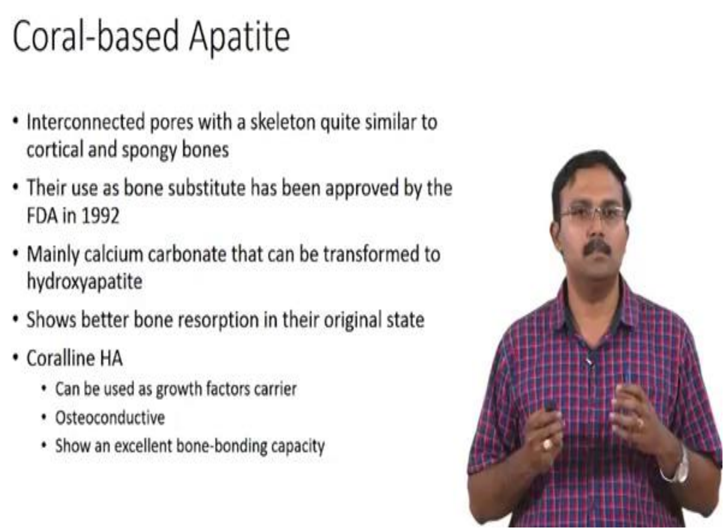

Coral-based Apatite

- Interconnected pores with a skeleton quite similar to cortical and spongy bones
- Their use as bone substitute has been approved by the FDA in 1992
- Mainly calcium carbonate that can be transformed to hydroxyapatite
- Shows better bone resorption in their original state
- Coralline HA
  - Can be used as growth factors carrier
  - Osteoconductive
  - Show an excellent bone-bonding capacity

Coral-based apatite is one of the older materials which were studied. These have interconnected pores with a skeleton, which is similar to the cortical and spongy bones of your body. This has been used as a bone substitute, and the FDA approved it in 1992, and people have tried to use this. This is primarily calcium carbonate that can be transformed into hydroxyapatite using some chemical reactions. This shows better bone resorption in its original state; if it is used as calcium carbonate, it shows better bone resorption.

Student: Can you explain what bone resorption is?

Bone resorption means it will be absorbed by your body. So, it gets replaced by the actual bone tissue.

Student: But the stitches which are there, which also get dissolved in a body. Are those resorbable?

Resorbable, yes.

Student: Yeah.

So yeah, they are also called resorbable sutures.

Student: Sutures.

So,

Student: Like how does that work? Does the body kind of make a bone over it, and then it will be dissolved like how? With these stitches are fine, stitches can just dissolve into the skin like this. Skin is already formed over there in the period. How will this work?

So, this also happens the same way. This is just like dissolving into the body. So, it gets absorbed by the body, and new bone gets deposited in the place. Depending on the rate of resorption and the rate of new bone formation, you will have a replacement with the original tissue and so on.

Coral-based hydroxyapatite can be used as growth factor carriers, and it is osteoconductive, and it shows excellent bone-bonding capacity in the sense that it can bind with the bone and form one entity.

Student: Conductive?

So, there are some terminologies which you should know osteoconductive and osteoinductive. Osteoconductive is when new bone can, bone ingrowth is allowed. Basically bones that are being formed can grow into the scaffold which you are placing. Osteoinductive is something that can trigger osteogenesis or new bone formation. So, osteoconductive materials are bioactive. Bioinert materials are not osteoconductive; they will just act as a barrier.

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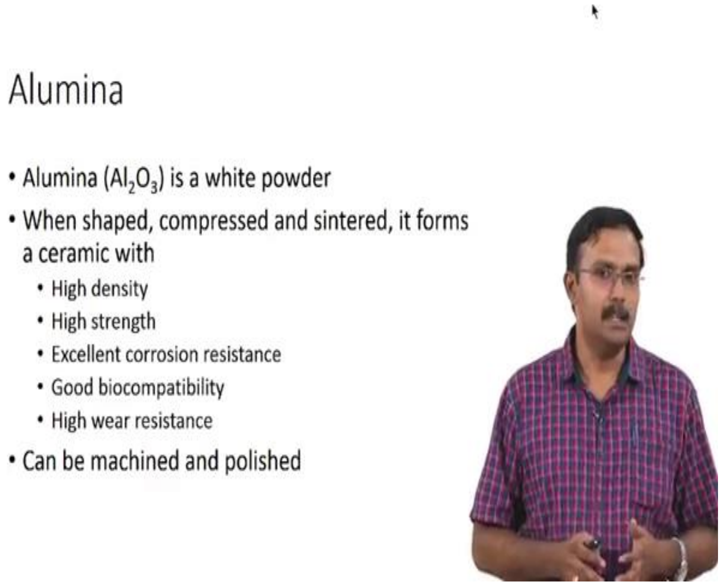

Alumina

- Alumina (Al_2O_3) is a white powder
- When shaped, compressed and sintered, it forms a ceramic with
  - High density
  - High strength
  - Excellent corrosion resistance
  - Good biocompatibility
  - High wear resistance
- Can be machined and polished

Alumina is a bioinert material, it is a white powder, and it can be shaped and compressed and sintered to form a ceramic, which has very high density and strength. It also has very good corrosion resistance and biocompatibility. It also has high water resistance. It can be machined and polished because of this reason; it is used in the hip joints.

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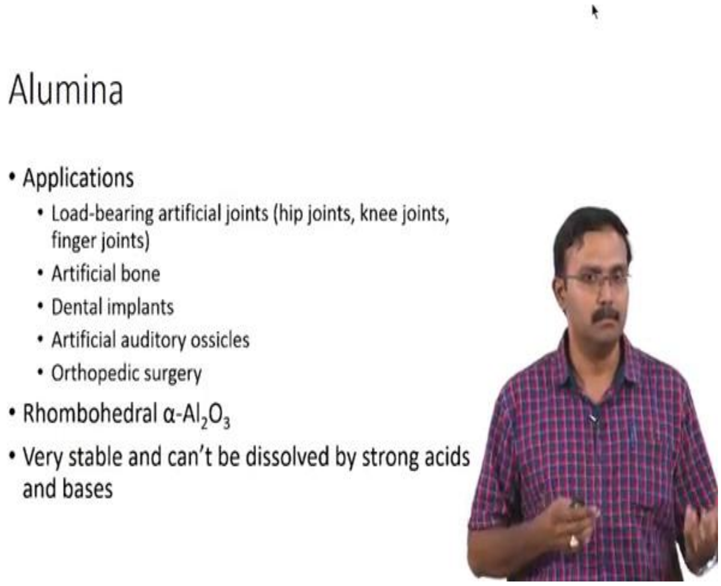

Alumina

- Applications
  - Load-bearing artificial joints (hip joints, knee joints, finger joints)
  - Artificial bone
  - Dental implants
  - Artificial auditory ossicles
  - Orthopedic surgery
- Rhombohedral α-Al_2O_3
- Very stable and can't be dissolved by strong acids and bases

If you remember some of the images, I had shown of the hip joints when we talked about the introduction. I would have shown some coating of ceramic on top of the ball and socket joints. These are usually alumina, and these have also been studied for artificial bones and dental implants and for artificial auditory ossicles and for orthopedic surgeries. There are different forms, different structures of alumina, and the rhombohedral alpha alumina is the one that has been used for biomedical applications. These are very stable and cannot be dissolved easily, even in strong acids and bases.

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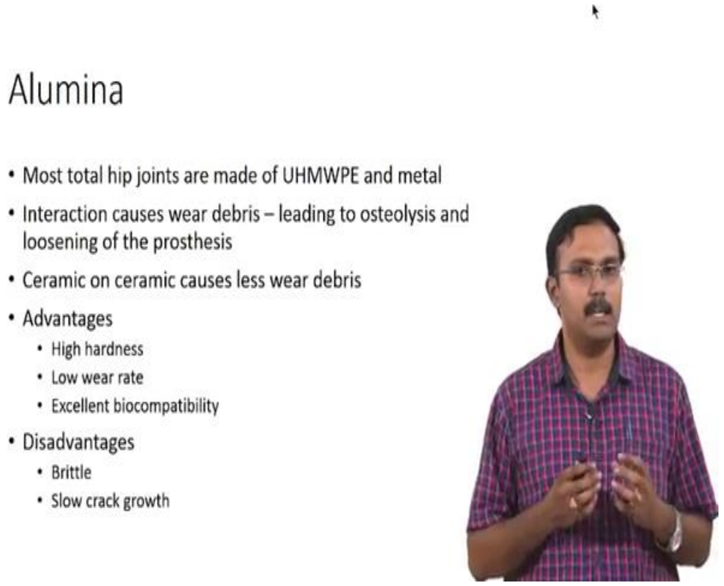

Alumina

- Most total hip joints are made of UHMWPE and metal
- Interaction causes wear debris – leading to osteolysis and loosening of the prosthesis
- Ceramic on ceramic causes less wear debris
- Advantages
  - High hardness
  - Low wear rate
  - Excellent biocompatibility
- Disadvantages
  - Brittle
  - Slow crack growth

Most hip replacement joints are made of ultra-high molecular weight polyethylene and metal. And what happens is, when you have these polymers to metal contact, there can be wear debris. These wear debris can lead to osteolysis, which is the lysis of bone cells, and this can lead to loosening of the prosthesis. This is called aseptic loosening. And this will lead to the failure or the replacement of the implant itself.

To avoid this, people are trying to use ceramic on ceramic joints. So, where you have a ceramic coating on both the socket and the ball. Thereby, you have lesser wear debris. Alumina has very good wear resistance because of this people have tried to use alumina coating for such applications. The advantages are, it has a very high hardness and a very low wear rate. It also has excellent biocompatibility; it does not cause any inflammatory responses. But the disadvantages are, it is brittle and can cause cracks because of this.

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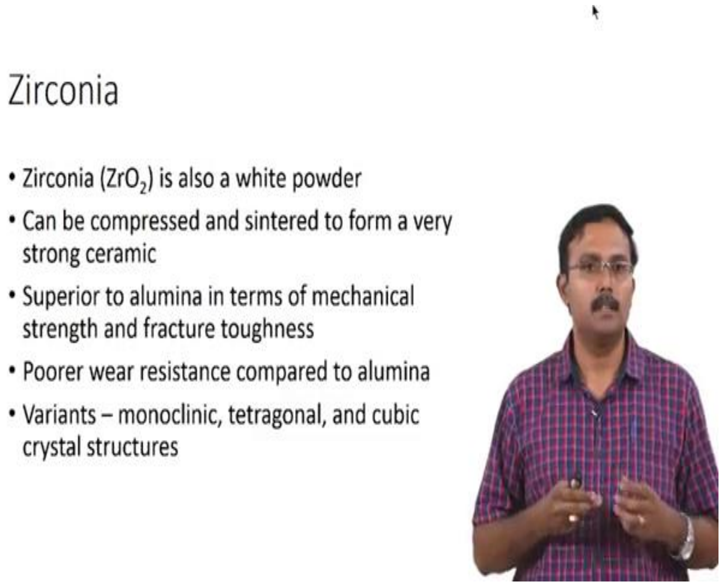

Zirconia

- Zirconia (ZrO_2) is also a white powder
- Can be compressed and sintered to form a very strong ceramic
- Superior to alumina in terms of mechanical strength and fracture toughness
- Poorer wear resistance compared to alumina
- Variants – monoclinic, tetragonal, and cubic crystal structures

Zirconia is another ceramic that is also a white powder; this can be compressed and sintered to form a strong ceramic. The mechanical strength itself is better than alumina. And it is fracture toughness is also better; however, it does not have the same wear resistance as alumina. When you have friction, it is going to cause more wear debris. Different variants have been used for zirconia implants. Phase transition can be done from metastable tetragonal grains to form a stable monoclinic phase. This causes an increase in volume and a reduction in compressive stress, which hinders the crack from continuing. So, this provides it is fracture toughness.

So, when you have this phase transition, whatever crack is formed does not progress. Only when the crack progress is going to cause bigger failure so, but this also decreases the mechanical strength of the material. People have tried to use partially stabilized zirconia where Yttria is doped along with zirconia and tried to use it as a stable variant of this zirconia ceramic. The presence of water can cause the phase transformation to happen more rapidly; this affects it is in vivo applications. Because of this, alumina has been used more extensively compared to zirconia.

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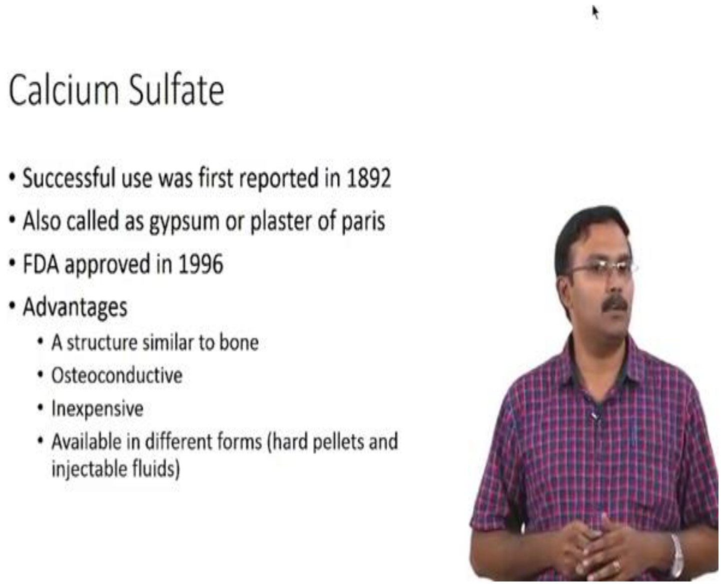

Calcium Sulfate

- Successful use was first reported in 1892
- Also called as gypsum or plaster of paris
- FDA approved in 1996
- Advantages
  - A structure similar to bone
  - Osteoconductive
  - Inexpensive
  - Available in different forms (hard pellets and injectable fluids)

Calcium sulfate is one of the most well studied and one of the earlier materials that was used. The first successful use of calcium sulfate was reported in 1892. It has been more than a century where people have been trying to use this. It is also called as gypsum or plaster of Paris. The FDA approved this in 1996. The advantages are it has a structural similarity to the bone; it is also osteoconductive, and it is very inexpensive. And it is available in different forms, either as hard pellets or as injectable fluids. Thereby, you can inject it into the site where you need to form a particular shape or structure.

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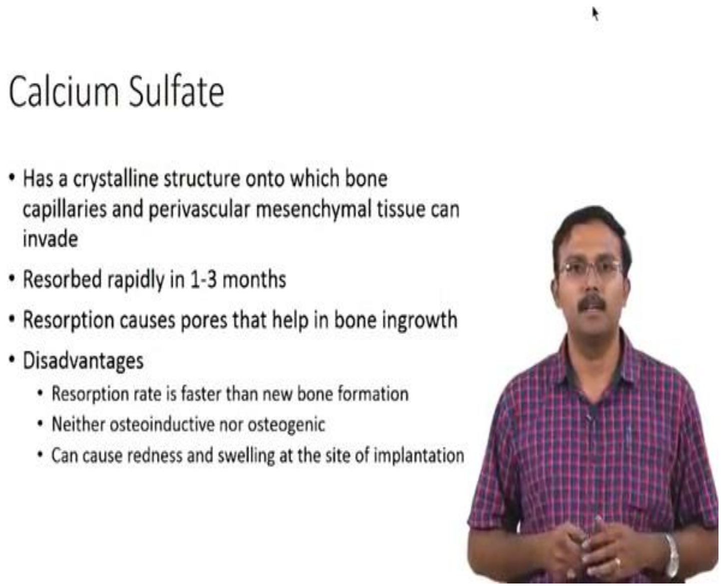

Calcium Sulfate

- Has a crystalline structure onto which bone capillaries and perivascular mesenchymal tissue can invade
- Resorbed rapidly in 1-3 months
- Resorption causes pores that help in bone ingrowth
- Disadvantages
  - Resorption rate is faster than new bone formation
  - Neither osteoinductive nor osteogenic
  - Can cause redness and swelling at the site of implantation

Calcium sulfate also has a crystalline structure onto which the bone capillaries and perivascular mesenchymal tissue can invade. So, this helps in integration with the body. It can be resorbed rapidly within 1 to 3 months. Resorption causes pores that can help in bone ingrowth. Usually, for bone ingrowth to happen, you need to have pores. And this resorption can create these pores, which can help in the bone ingrowth. However, this resorption rate is very fast, so bone formation takes up to 4 months, and resorption of calcium sulfate can start within a month or so. So, this means it cannot be used, where you need new bone growth before this can be removed.

Student: So, the ideal state would be well; both of these are balanced.

Yeah, it has to be comparable. So, you can have the resorption to be slower than new bone growth formation, provided it is not causing any negative effects. So, then it would not be a problem. You can have something there, and it will still integrate well with your body. But if it is faster, than you have a problem.

This is neither nor osteoinductive or osteogenic; in the sense that it does not trigger new bone formation, it only helps in bone ingrowth. This can also cause redness and swelling at the site of implantation, which can cause discomfort and serious pain, which would lead to failure of implants.

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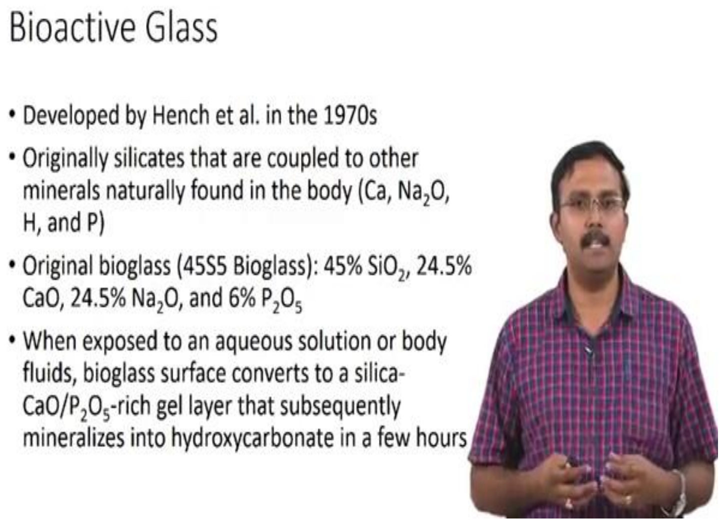

Bioactive Glass

- Developed by Hench et al. in the 1970s
- Originally silicates that are coupled to other minerals naturally found in the body (Ca, Na_2O, H, and P)
- Original bioglass (45S5 Bioglass): 45% SiO_2, 24.5% CaO, 24.5% Na_2O, and 6% P_2O_5
- When exposed to an aqueous solution or body fluids, bioglass surface converts to a silica-CaO/P_2O_5-rich gel layer that subsequently mineralizes into hydroxycarbonate in a few hours

Bioactive glasses material is a ceramic that was developed in the 1970s, and originally, silicates were coupled with other minerals that are present in your body like calcium, sodium oxide, hydrogen, and phosphorous. The original bioglass, which is the 45S5 bioglass, contains 45% silica, 24.5% calcium oxide, 24.5% sodium oxide and 6% phosphorus pentoxide. This bioglass has been bioactive and it has been used for different applications.

When exposed to an aqueous solution or body fluids, what happens is, the surface of this bioglass has the silica, calcium oxide, and phosphorus pentoxide rich gel layer, which is formed. And this gel layer is subsequently mineralized to form a hydroxycarbonate within a few hours of implantation. So, because of this, it promotes bone ingrowth.

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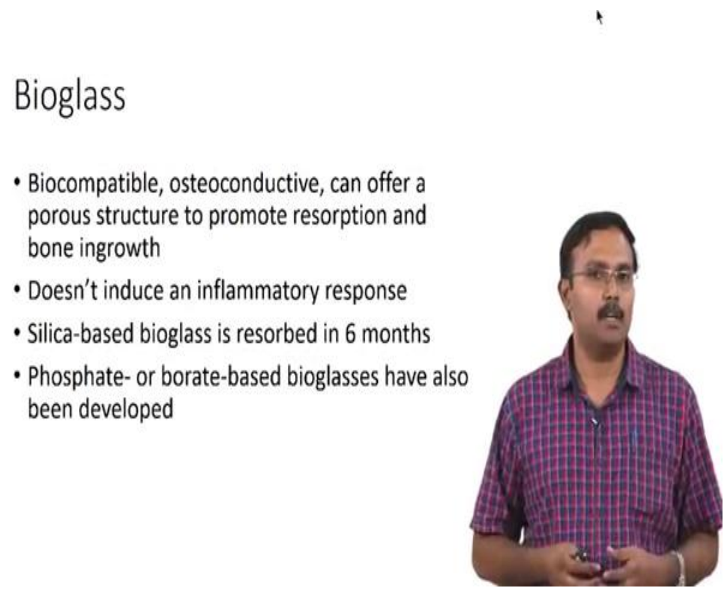

Bioglass

- Biocompatible, osteoconductive, can offer a porous structure to promote resorption and bone ingrowth
- Doesn’t induce an inflammatory response
- Silica-based bioglass is resorbed in 6 months
- Phosphate- or borate-based bioglasses have also been developed

It is biocompatible and osteoconductive; it can offer a porous structure that will promote resorption and bone ingrowth. The porosity itself can be achieved with a way you fabricate the material. This does not induce any inflammatory response, and silica-based bioglass is usually resorbed in about six months. Phosphate and borate-based bioglasses have also been developed, and they are also being studied.

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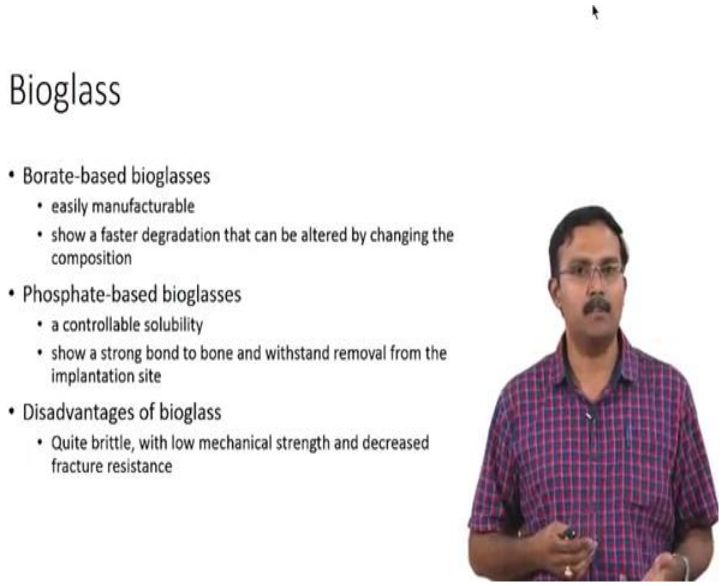

Bioglass

- Borate-based bioglasses
  - easily manufacturable
  - show a faster degradation that can be altered by changing the composition
- Phosphate-based bioglasses
  - a controllable solubility
  - show a strong bond to bone and withstand removal from the implantation site
- Disadvantages of bioglass
  - Quite brittle, with low mechanical strength and decreased fracture resistance

Borate based bioglasses are easy to manufacture, and they show faster degradation; however, this degradation can be altered by changing the composition of the material itself. Phosphate based bioglasses have controllable solubility, which makes them desirable for your applications because you can tailor the way the material gets resorbed. They show a strong bond to the bone and can withstand the stresses in the site of implantation.

The disadvantage itself is, it is quite brittle; all these bioglasses are quite brittle and have very low mechanical strength and decreased fracture resistance. This is a glass, right? It is a type of glass, so it is going to be brittle. It does not mean you cannot use it; you cannot use it in load-bearing applications, or you would have to judiciously use it for specific applications and specific sites. And you might have to fabricate it in a way that it will be suitable or use it along with other materials to provide the desired mechanical properties.

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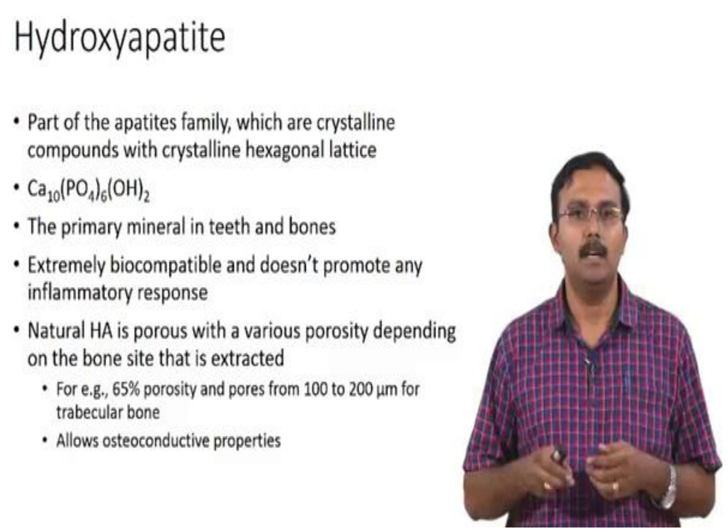

Hydroxyapatite

- Part of the apatites family, which are crystalline compounds with crystalline hexagonal lattice
- $Ca_{10}(PO_4)_6(OH)_2$
- The primary mineral in teeth and bones
- Extremely biocompatible and doesn't promote any inflammatory response
- Natural HA is porous with a various porosity depending on the bone site that is extracted
  - For e.g., 65% porosity and pores from 100 to 200 μm for trabecular bone
  - Allows osteoconductive properties

Hydroxyapatite is the most commonly used material today because hydroxyapatites are part of the apatite family, which are crystalline with a hexagonal lattice. They have a specific chemical formula, which is $Ca_{10}(PO_4)_6(OH)_2$. It has a calcium to phosphorous ratio of 1.67. So, that is characteristic of hydroxyapatite.

Hydroxyapatite is what is present in your body. The mineral which is present in your bone and teeth is hydroxyapatite. So, because of this, it is extremely biocompatible and does not cause any inflammatory response. So, you can use it for bone and dental tissue engineering without any issues. You can have natural hydroxyapatite or synthetic hydroxyapatite.

The natural hydroxyapatite is porous with the porosity depending on where it is being extracted from. If you are going to take hydroxyapatite from trabecular bone, it is going to have about 65 percent porosity with pores ranging from 100 to 200 micrometers in size. So, these pores help in the osteoconductive property of hydroxyapatite.

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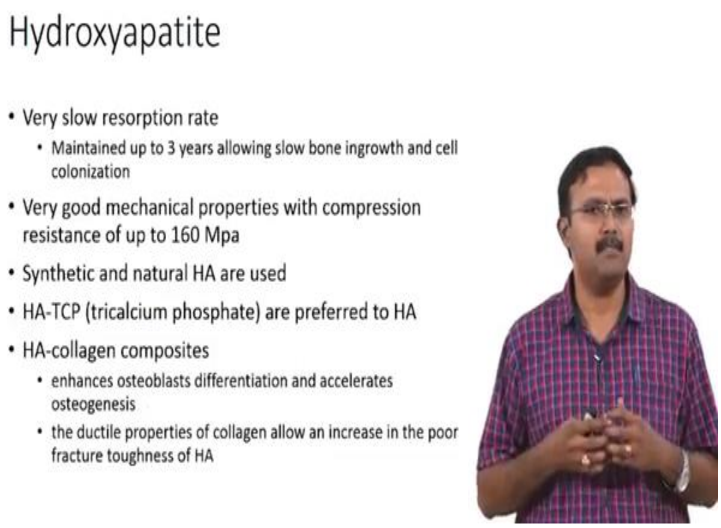

Hydroxyapatite

- Very slow resorption rate
  - Maintained up to 3 years allowing slow bone ingrowth and cell colonization
- Very good mechanical properties with compression resistance of up to 160 Mpa
- Synthetic and natural HA are used
- HA-TCP (tricalcium phosphate) are preferred to HA
- HA-collagen composites
  - enhances osteoblasts differentiation and accelerates osteogenesis
  - the ductile properties of collagen allow an increase in the poor fracture toughness of HA

They have a very slow resorption rate. They are going to be present in your body for a long time; they can be maintained in your body for up to 3 years. And this allows slow bone ingrowth and cell colonization. Because it is hydroxyapatite, which is present in your body; It is going to integrate very nicely with your body as well. It is going to bind with the bone and become a part of the new bone itself.

It has very good mechanical properties with compression stresses, which are close to 160 MPa. So, which is good, but still not as good as your bone. Your bone compression stresses are usually in 10 to 30 GPa. So, this has very good properties. Synthetic and natural HA has been used. To get better properties, what people try to do is use hydroxyapatite along with tricalcium phosphate. This mixture, which is called biphasic calcium phosphate, is preferred to using general hydroxyapatite or tricalcium phosphate independently.

People have also tried using hydroxyapatite collagen composites, which is what your bones ECM. So, your bone ECM primarily contains collagen and hydroxyapatite. This enhances osteoblasts differentiation and promotes osteogenesis and improving new bone formation. The ductile properties of collagen make sure it can be prepared in the shapes, and it provides mechanical properties that are desirable for the bone itself. You can prepare these nanocomposites where hydroxyapatite nanoparticles are prepared and dispersed in collagen. Thereby, you get structures that are very close to what your bone tissue would be.

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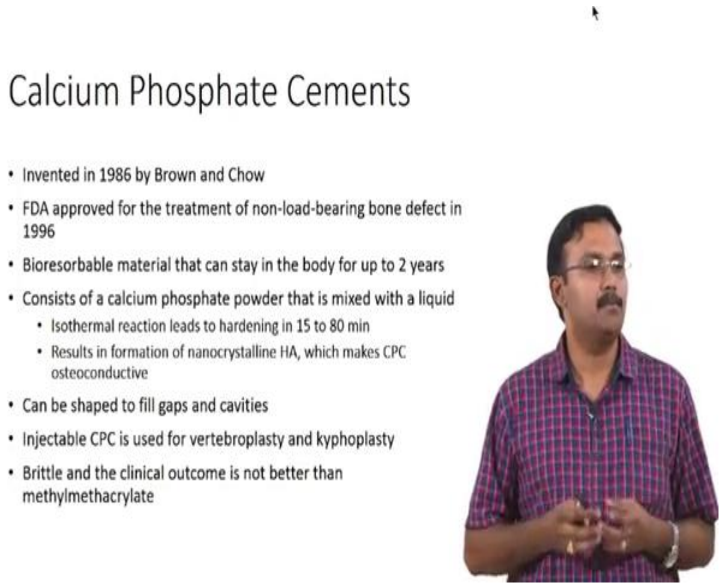

Calcium Phosphate Cements

- Invented in 1986 by Brown and Chow
- FDA approved for the treatment of non-load-bearing bone defect in 1996
- Bioresorbable material that can stay in the body for up to 2 years
- Consists of a calcium phosphate powder that is mixed with a liquid
  - Isothermal reaction leads to hardening in 15 to 80 min
  - Results in formation of nanocrystalline HA, which makes CPC osteoconductive
- Can be shaped to fill gaps and cavities
- Injectable CPC is used for vertebroplasty and kyphoplasty
- Brittle and the clinical outcome is not better than methylmethacrylate

Calcium phosphates cement were invented in 1986, and this was approved for non-load bearing bone defect treatment in 1996. These are bioresorbable materials that can stay in your body for about two years. These consist of calcium phosphate powder, which is mixed with a liquid, and there is an isothermal reaction leading to the hardening of this in 15 minutes to about 80 minutes. So, this is what is used in your dental fillings and so on.

After the reaction, it results in the formation of nanocrystalline hydroxyapatite, which makes the calcium phosphate cements osteoconductive. The advantage of using these is, it can be used to fill gaps and cavities. Since it is a paste, it will fill and take the shape of the cavity in which you have used it.

Injectable cement has also been used for vertebroplasty and kyphoplasty, which are injuries to your spinal bones and your disc problems; like if we have a compression fracture of your spine, then these kinds of cement have been used; so that it can be used for healing the fracture. These are brittle, and the clinical outcome is not better than that of methylmethacrylate. Because of this, people still sometimes preferred to use polymethyl methacrylate (PMMA) kinds of alternatives instead of cement.

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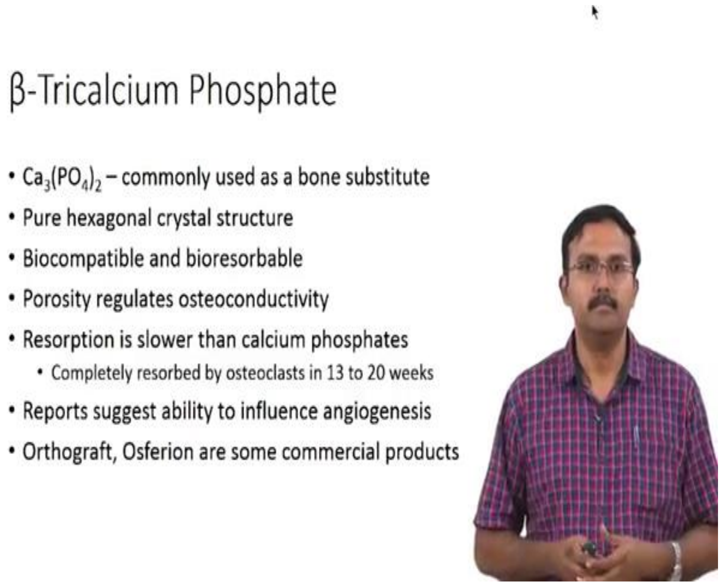

β-Tricalcium Phosphate

- $Ca_3(PO_4)_2$ – commonly used as a bone substitute
- Pure hexagonal crystal structure
- Biocompatible and bioresorbable
- Porosity regulates osteoconductivity
- Resorption is slower than calcium phosphates
  - Completely resorbed by osteoclasts in 13 to 20 weeks
- Reports suggest ability to influence angiogenesis
- Orthograft, Osferion are some commercial products

β-Tricalcium phosphate is the most commonly used bone substitute; it is a pure hexagonal crystal structure with high biocompatibility and bioresorbability. The porosity regulates the osteoconductivity of this material, and the resorption is slower than other calcium phosphates; however, it gets completely resorbed in about 13 to 20 weeks; this is faster than hydroxyapatite do. Reports suggest that they have the ability to influence angiogenesis as well.

Bone is a very highly vascular tissue. It has a lot of blood vessels, and it is important to create a bone substitute that would have these vascular networks. So, β-Tricalcium phosphate has indicated that it can influence how the angiogenesis happens. Some of the commercial materials which use β-Tricalcium phosphate, are Orthograft and Osferion. So, these are used for bone replacements and regeneration.

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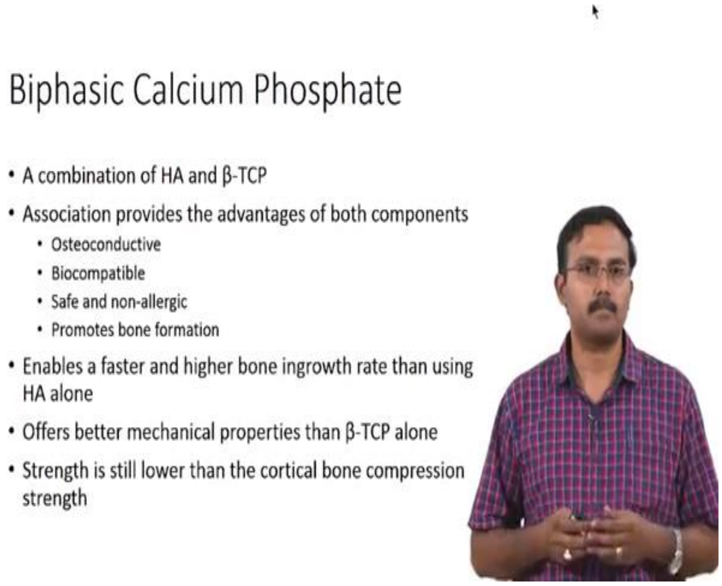

Biphasic Calcium Phosphate

- A combination of HA and β-TCP
- Association provides the advantages of both components
  - Osteoconductive
  - Biocompatible
  - Safe and non-allergic
  - Promotes bone formation
- Enables a faster and higher bone ingrowth rate than using HA alone
- Offers better mechanical properties than β-TCP alone
- Strength is still lower than the cortical bone compression strength

The biphasic calcium phosphate is a combination of hydroxyapatite and β-Tricalcium phosphate. It is preferred than HA or β-Tricalcium phosphate being used independently. So, this has the advantages of both these materials. It is highly osteoconductive, biocompatible; it is safe and nonallergic. It also promotes new bone formation, so in a sense, it is osteoinductive. It enables faster and higher bone ingrowth rate compared to hydroxyapatite alone. It offers better mechanical properties than β-Tricalcium phosphate alone. The strength is still lower than the cortical bones compression strength. So, optimizing this to get desirable mechanical properties is always a challenge.

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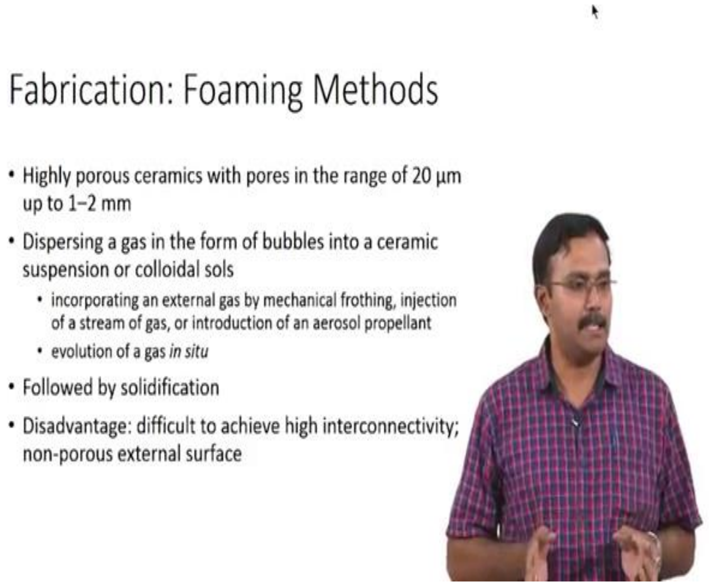

Fabrication: Foaming Methods

- Highly porous ceramics with pores in the range of 20 µm up to 1–2 mm
- Dispersing a gas in the form of bubbles into a ceramic suspension or colloidal sols
  - incorporating an external gas by mechanical frothing, injection of a stream of gas, or introduction of an aerosol propellant
  - evolution of a gas *in situ*
- Followed by solidification
- Disadvantage: difficult to achieve high interconnectivity; non-porous external surface

We looked at different fabrication techniques for scaffolds earlier. The techniques which we looked at were all primarily for polymers. So, those are scaffolds that we can prepare from different types of polymers. Similarly, for ceramics, there are different techniques that can be employed, and we will just quickly go through some of the techniques.

One of the most common techniques is the foaming method. As I said, porosity is crucial for ceramics because that is what will regulate osteoconductivity. Bone ingrowth will happen when you have a porous structure.

The techniques which we will be looking at will have the ability to create these porous structures. The foaming method is capable of producing highly porous ceramics with pores, which can range from 20 μm to up to 1 - 2 mm. So, what happens here is, you disperse a gas in the form of bubbles into a ceramic suspension or colloidal solution. And this is done by incorporating an external gas by mechanical frothing or by injection of a stream of gas along with this suspension or introduction of aerosol propellant. You can also create the evolution of gas in situ either through in situ polymerization or techniques like that.

So, this suspension is then solidified, and eventually, the gases are released, the foaming agent is released, thereby creating porous structures. This is similar to one of the techniques which we looked at for polymers. Where again, you used things like ammonium carbonate where carbon dioxide can come out, creating the pores. The disadvantage is, it is difficult to achieve high pore interconnectivity, and also there is a non-porous external surface. The pores are present only on the inside, and it might not be present on the surface, which can cause problems. You need to have a porous surface for the bone ingrowth to be better and for cell infiltration to happen.

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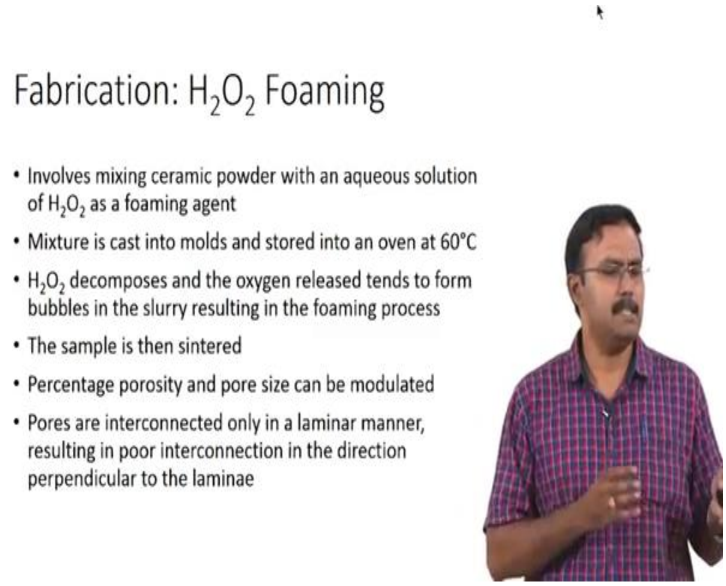

Fabrication: H_2O_2 Foaming

- Involves mixing ceramic powder with an aqueous solution of H_2O_2 as a foaming agent
- Mixture is cast into molds and stored into an oven at 60°C
- H_2O_2 decomposes and the oxygen released tends to form bubbles in the slurry resulting in the foaming process
- The sample is then sintered
- Percentage porosity and pore size can be modulated
- Pores are interconnected only in a laminar manner, resulting in poor interconnection in the direction perpendicular to the laminae

Amongst these foaming methods, there are a few different types. H_2O_2 foaming is one of the more commonly studied and a simpler technique to use. So, what is done here is the ceramic powder mixed with an aqueous solution of H_2O_2, where H_2O_2 is the foaming agent. The mixture is cast into molds and stored in an oven at 60 °C. The H_2O_2 decomposes, and oxygen is released in the form of bubbles in the slurry, which causes the foaming process. And as these bubbles come out, you create the pores. And finally, the sample is sintered, and the percentage porosity and the pore size can be modulated by using different concentrations of H_2O_2 and so on. The pores are interconnected only in a laminar manner, which results in poor interconnection in the direction which is perpendicular to the laminae. So, it can only be connected in one direction.

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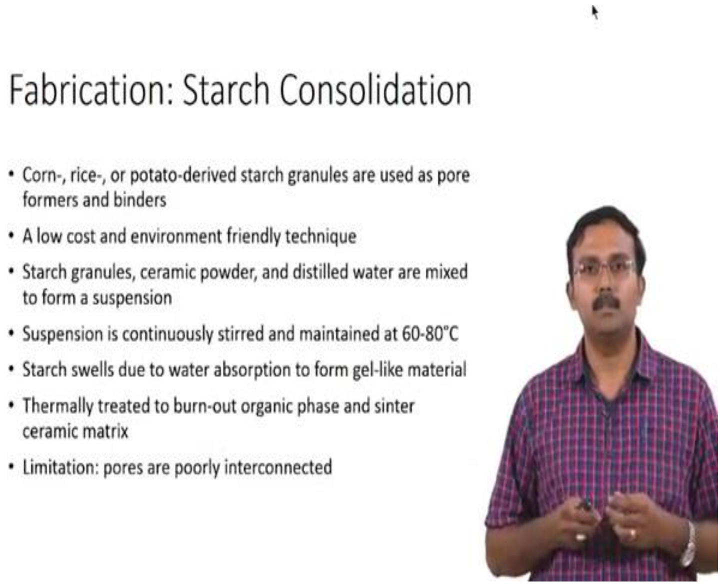

Fabrication: Starch Consolidation

- Corn-, rice-, or potato-derived starch granules are used as pore formers and binders
- A low cost and environment friendly technique
- Starch granules, ceramic powder, and distilled water are mixed to form a suspension
- Suspension is continuously stirred and maintained at 60-80°C
- Starch swells due to water absorption to form gel-like material
- Thermally treated to burn-out organic phase and sinter ceramic matrix
- Limitation: pores are poorly interconnected

Another technique that is used, which is an eco-friendly technique, is the starch consolidation technique. Corn, rice, or potato derived starch granules are used as pore formers and binders. So, what is done is, the starch granules, ceramic powder, and water are mixed to form a suspension. And the suspension is continuously stirred and maintained at 60 to 80 °C. And finally, these are cast where the starch starts swelling because starch can absorb a lot of water and forms a gel-like material.

Then it is thermally treated. In a sense, it is heated to burn out the organic phase and sinter the ceramic phase. Because of the starch granules which occupy the cavities in between where the ceramic is sintered, you will have pores that are formed. However, the pores are not interconnected in this case. Because only the starch granules occupy the pores, and there is no way to create interconnected pores.

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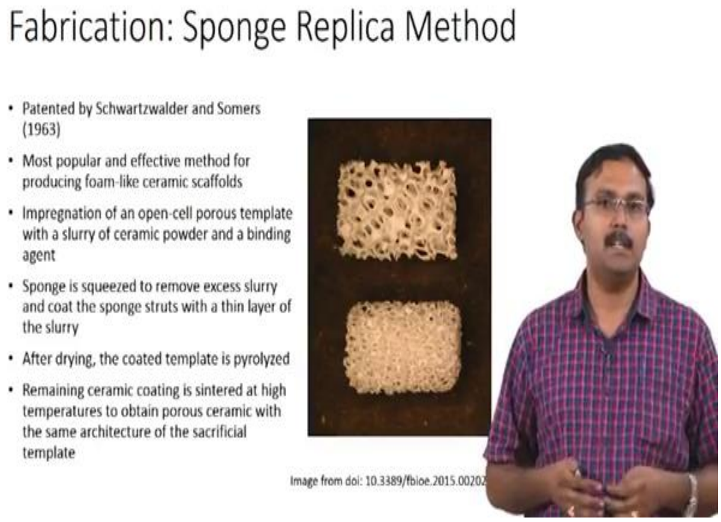

Fabrication: Sponge Replica Method

- Patented by Schwartzwalder and Somers (1963)
- Most popular and effective method for producing foam-like ceramic scaffolds
- Impregnation of an open-cell porous template with a slurry of ceramic powder and a binding agent
- Sponge is squeezed to remove excess slurry and coat the sponge struts with a thin layer of the slurry
- After drying, the coated template is pyrolyzed
- Remaining ceramic coating is sintered at high temperatures to obtain porous ceramic with the same architecture of the sacrificial template

Image from doi: 10.3389/fbioe.2015.00202

The sponge replica method is the most common method which is used for commercial materials. What you see here are commercial bone grafts, which are manufactured using the sponge replica method. The technique itself was patented in 1963, and this has been quite popular and very effective. What you do is, you impregnate an open-cell porous template with a slurry of ceramic powder and a binding agent. So, you first create a template, the shape in which you want to create the scaffold.

This is usually made out of some natural or synthetic polymer. You then load it along with the ceramic slurry, which is present along with it. And the sponge is squeezed to remove any excess slurry. And the ceramic is used to coat the sponge on the struts, and the curves as a thin layer. And then, this is dried, and then the coated template is pyrolyzed to remove the sacrificial template.

So, now you have only the ceramic which is remaining. You create a positive mold. So, whatever mold you created, you have the exact shape in the form of ceramic. This ceramic coating is sintered at high temperatures. So, that you get the porous ceramic with the same architecture, and during sintering, the sacrificial template is lost.

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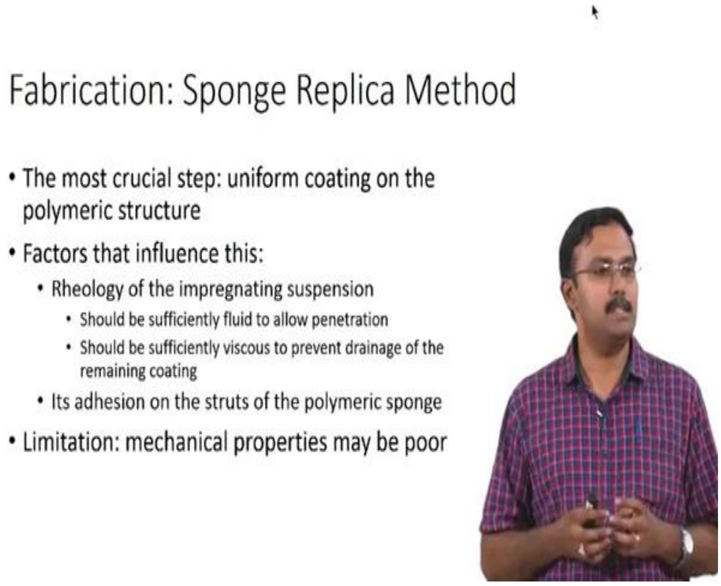

Fabrication: Sponge Replica Method

- The most crucial step: uniform coating on the polymeric structure
- Factors that influence this:
  - Rheology of the impregnating suspension
    - Should be sufficiently fluid to allow penetration
    - Should be sufficiently viscous to prevent drainage of the remaining coating
  - Its adhesion on the struts of the polymeric sponge
- Limitation: mechanical properties may be poor

The most crucial step in this sponge replica method is to get the uniform coating on the polymeric structure. Because if you have a non-uniform coating, then you are not going to reproduce the same structure. So, the factors which influence this are the rheology of the material and how well this suspension can adhere to the struts in the sacrificial template.

The rheology is crucial because the suspension needs to be sufficiently fluid for it to allow penetration. It needs to reach all the areas of the template so that it can coat it completely. At the same time, it needs to be sufficiently viscous so that it does not just drain off after coating. So, after coating it needs to stick there and remain there. That will happen only if you have the right viscosity. The limitation with this method is you may not get desirable mechanical properties; you would get something which is slightly weak.

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Fabrication: Solid Freeform Fabrication

- Also referred to as rapid prototyping
- Moldless techniques that use layer-wise manufacturing directly from computer-generated 3D models
- Common SFF strategies
  - Stereolithography (SLA) uses a blend of ceramic powders and photocurable monomer
  - Selective laser sintering (SLS) employs a CO_2 laser beam to sinter thin layers of powdered ceramic materials to form 3-D objects
  - Powder-based 3D printing technology

Other than these techniques, you also have solid freeform fabrication techniques. So, these are broadly called as the rapid prototyping techniques. These are moldless technologies where people use layer by layer deposition using computer-generated 3D models. There are different strategies such as stereolithography, selective laser sintering, and powder-based 3D printing are the most common ones which have been used. And all of them seem to have their own advantages and disadvantages.

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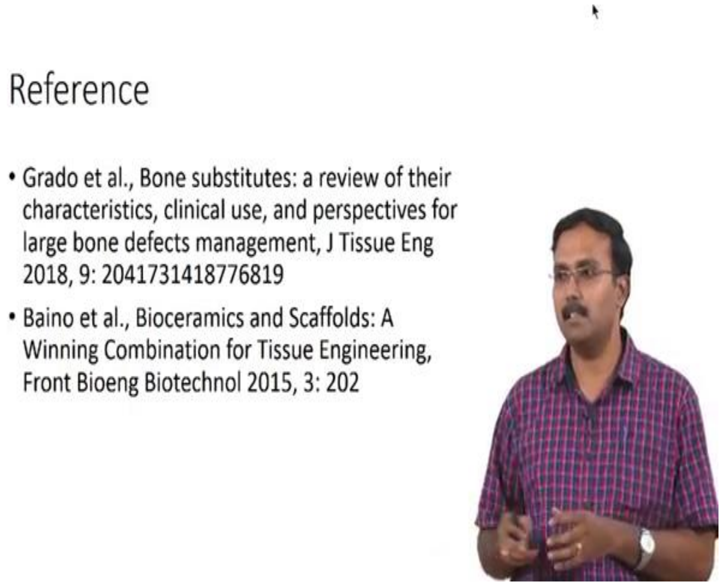

Reference

- Grado et al., Bone substitutes: a review of their characteristics, clinical use, and perspectives for large bone defects management, J Tissue Eng 2018, 9: 2041731418776819
- Baino et al., Bioceramics and Scaffolds: A Winning Combination for Tissue Engineering, Front Bioeng Biotechnol 2015, 3: 202

I am not going to go into details of the advantages and disadvantages, but you can go through these review articles. I think I have already uploaded them I am not sure, but if not, I will upload them today. These review articles and book chapters give you enough information about ceramics, and I have given you an overview of what ceramics are. With these, we come to the end of the different materials which are used as scaffolds. So, we will talk about cells, the cell sources, cell types that can be used, and also tissue homeostasis regarding cell adhesion, migration, proliferation, and so on in the next few classes.

So, thank you.