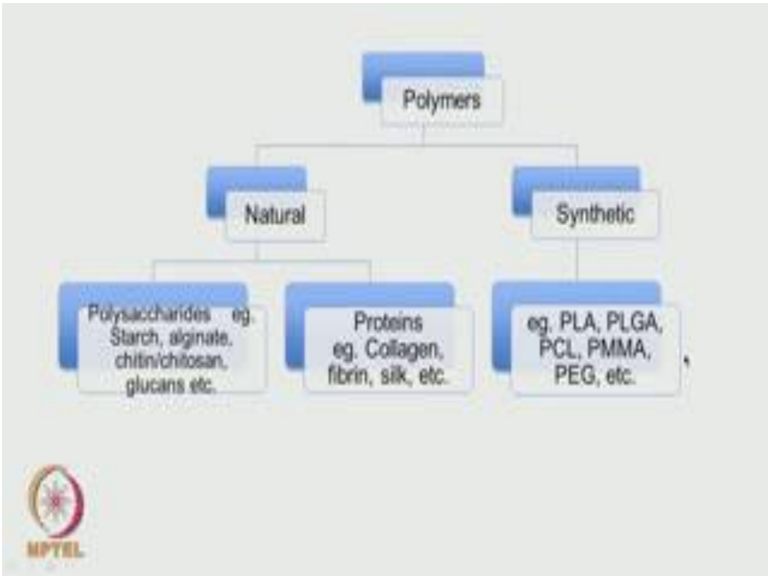
Medical Biomaterials
Prof. Mukesh Doble
Department of Biotechnology
Indian Institute of Technology, Madras

Lecture - 33
Natural/Biopolymers

Hello everyone, welcome to the course on medical biomaterials. We will continue on the topic of biopolymers or natural polymers. They seem to have very good their future in design of novel biomaterials with in conjunction with synthetic polymers or even with the metals ceramics and so on actually.

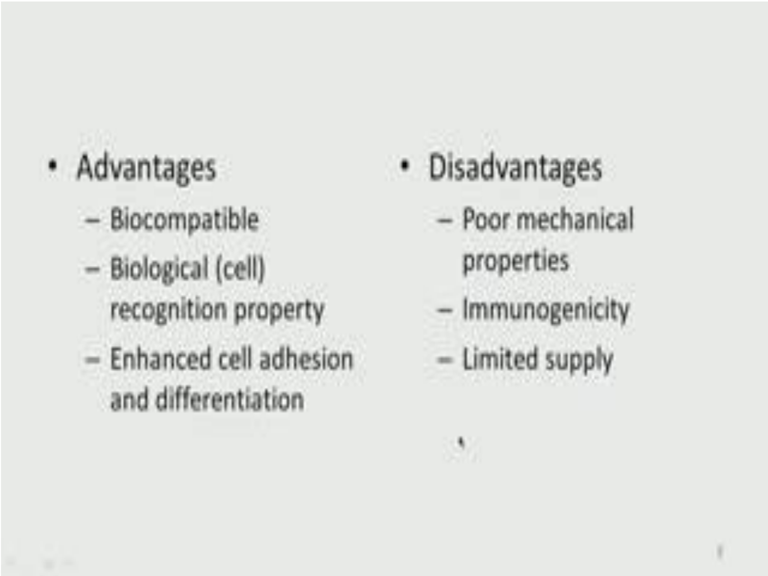
(Refer Slide Time: 00:35)



So, we saw this slide in the previous class. So, we have the natural polymers we have the synthetic polymers. So, synthetic polymers could be polylactic acid, polylactic glycolic acid, polycaprolactone, polymethyl methacrylate, polyethylene glycol and so on. So, these are all synthetic; that means, you synthesize them in the lab then we have the natural; that means, they come from the plants or they come from bacteria fungi animals and so on.

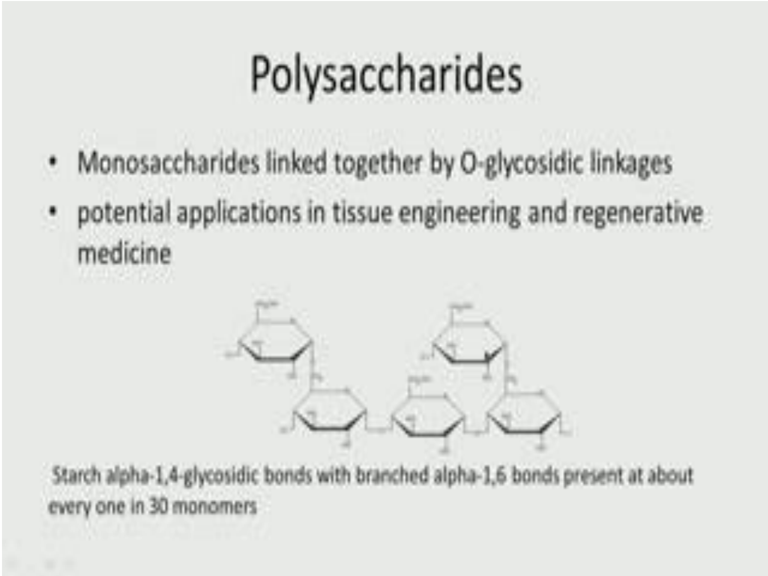
So, here we have 2 types the polysaccharides, the proteins; polysaccharides as the name implies and it contains different types of sugars in a polymeric form. So, it could be starch, alginate, chitosan, chitin, glucans then hyaluronic acid and so on. Now other type is protein; that means, they have the amide bond, C double bond O N that is the C double bond O amide bond. So, it could be collagen fibrin silk all those come under this category. So, all these are called natural polymers they have many advantages. So, one would like to make use of them they are biocompatible these biological recognition property; that means, cells are able to recognize them as compatible material. So, generally the cell adhesion differentiation is excellent when compared to synthetic polymers.

(Refer Slide Time: 02:06)



But they also have disadvantages poor mechanical properties they have immunogenic issues like if you are taking material from animals and can be have contamination toxicity then limited supply we cannot produce it in large supply like say polyethylene or polypropylene or polymethyl methacrylate in an industry so; obviously, there is a limited supply.

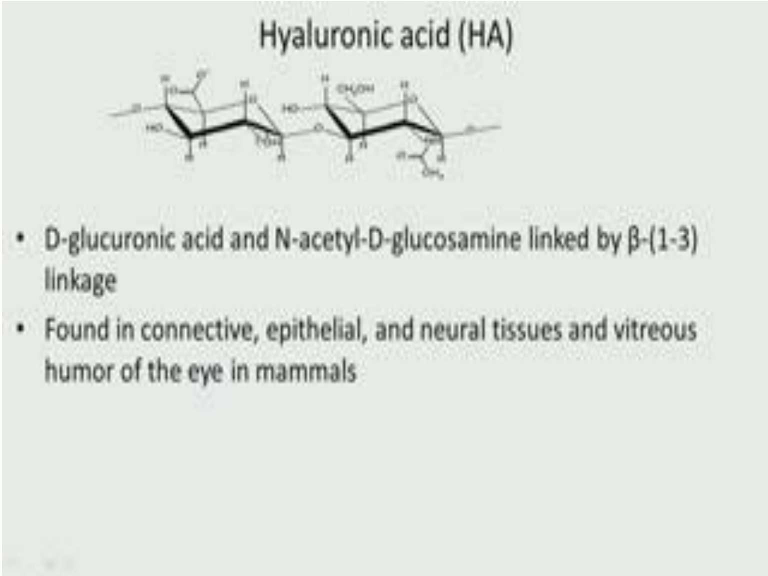
(Refer Slide Time: 02:29)



So, the polysaccharides we saw; that means, they are made up of monosaccharides like this then this is called a glycosidic linkage; O glycosidic linkage. So, we call this as 1 4 because this is 1 and this is 4 and this is called 1 6 linkage because we have the 1 here and the 6 here and these are called the alpha; alpha means the voyage which forms the bond is below these sacred whereas, if the OH comes about then we call it the beta linkage.

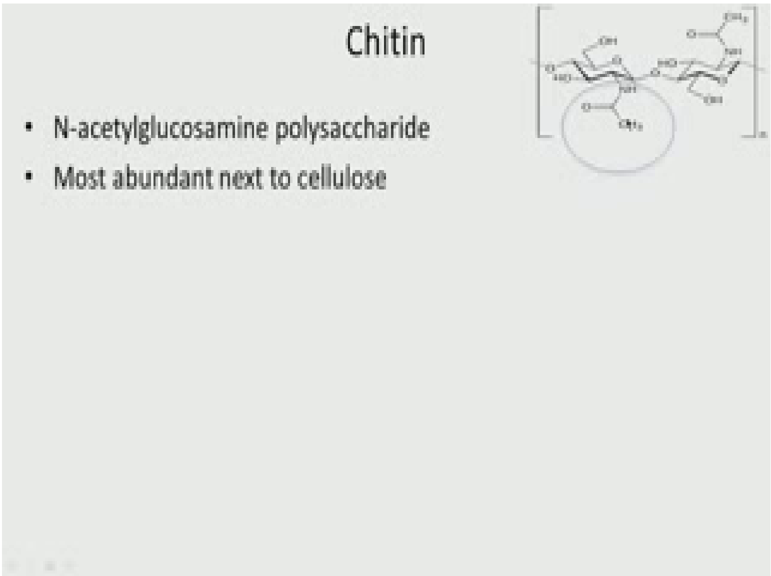
So, there are different types of polysaccharides we can have alpha linkage beta linkage we can have 1 4 1 6 1 3. So, different types of linkages different types of sugars saccharides where you end up having a large variety of polymers of this type. So, starch for example, has got this alpha one 4 linkage and this one 6 happens once in thirty. So, when we have one six; obviously, you are going to have the branching if it is totally one 4 then it is going to be very linear and crystalline when you have branching it becomes a little bit amorphous less crystalline.

(Refer Slide Time: 03:48)



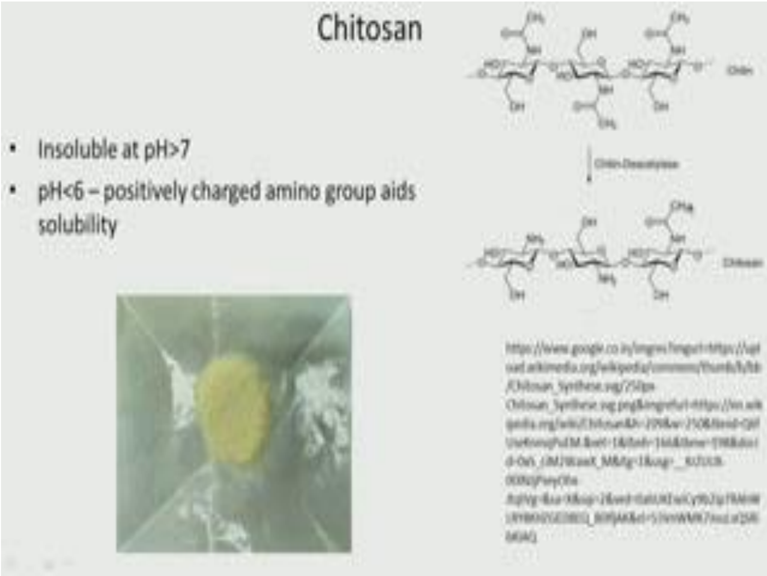
Hyaluronic acid this is produced by bacteria it is found in connective tissues epithelial humor of the eyes in mammal neural tissues. So, it is a very important polymer called hyaluronic acid. So, we have the D glucuronic; D glucuronic that is the acid glucuronic and n acetyl glucosamine. So, we have the amine here we have the acetyl CH 3, CO group here and they are linked by beta unlike the alpha which is down beta is up. So, this is how the hyaluronic acid is found.

(Refer Slide Time: 04:28)



Then we also looked at chitin; chitin as you can see has this acetyl in the nitrogen i mean connected. So, its N acetyl glucosamine polysaccharide it is most abundant next to cellulose it is very useful.

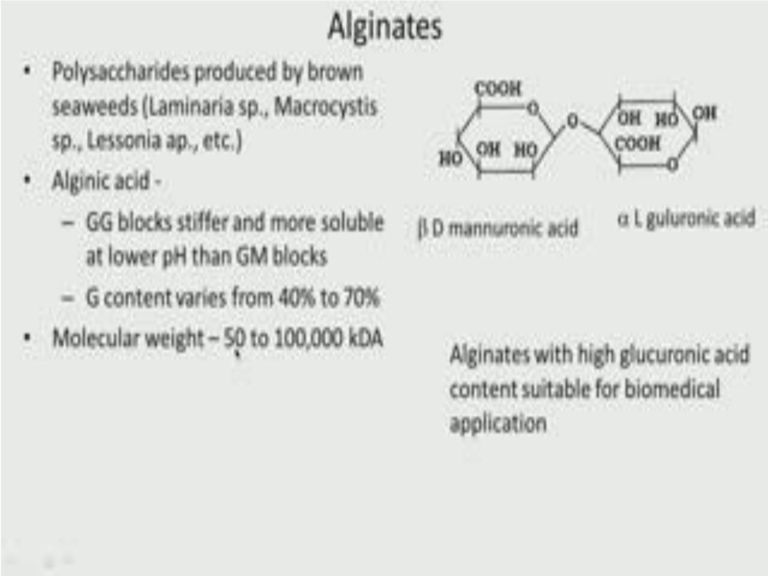
(Refer Slide Time: 04:47)



Then we saw Chitosan, you produce Chitosan from chitin; that means, you remove this acetyl group using air D acetyl cysteine. So, you end up having an H 2. So, this is highly water soluble and depending upon the degree of removal of acid deacetylation we can have the solubility very high or very low and so on actually whereas, a chitin is not soluble. So, this is a sort of a morphological picture of chitosan.

Its insoluble at p H greater than 7, but at p H less than 6 positively charged this amino groups increases the solubility. So, this is deacetylation alginate.

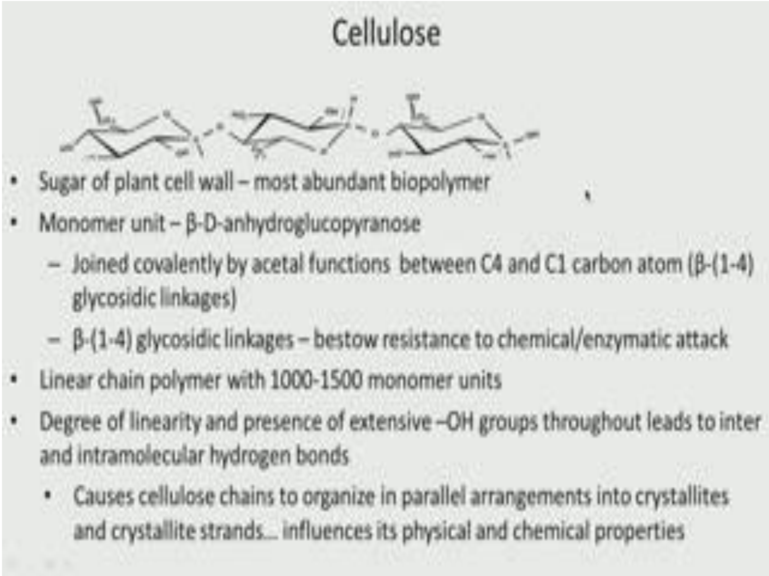
(Refer Slide Time: 05:31)



So, alginates alginic acid and so on guar gum for example,. So, it contains mannuronic acid connected by guluronic acid with a beta linkage as you can see this is a beta linkage. So, those with high guluronic acid content are used good for my biomedical application because they are stiff when the; this guluronic acid amount goes down then it loses its stiffness. So, these are produced by brown seaweeds several types of brown seaweeds. So, this gives the stiffness more soluble at lower p H than GM block.

So, the g content can vary between 40 to 70 percent and the molecular weight is 50 to 100,000 kilo Dalton. So, alginates can be used for drug encapsulation.

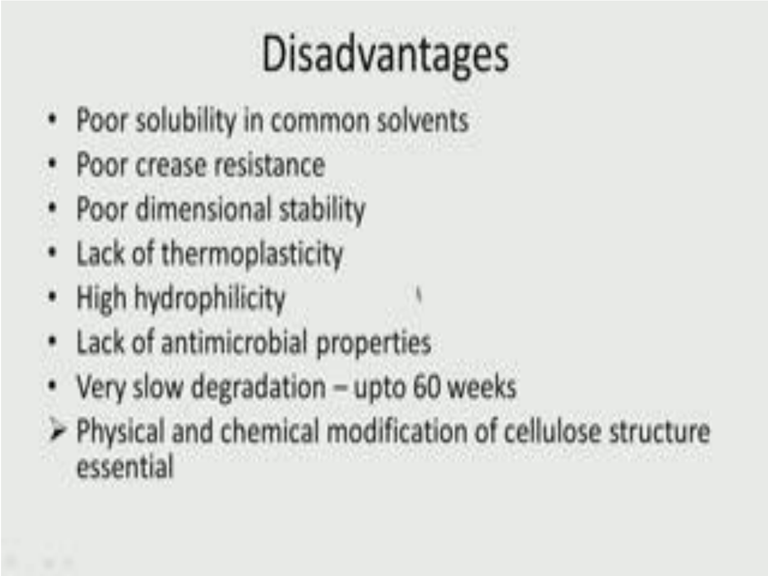
(Refer Slide Time: 06:24)



Cellulose; this is what cellulose is they are all connected like this. So, they are found in cell wall of the plants its most abundant biopolymer most abundant biopolymer. So, we have the anhydroglucopyranose, here anhydroglucopyranose as you can see here and they are connected by this beta linkage here join the covalently by acetyl functions between the C4 and the C1. So, they are connected by the C 4 and C1 and carbon beta 1 4 glycosidic. So, the beta 1 4 glycosidic linkage the beta 1 4, this is 1 and this is 4 bestow resistance to chemical an enzymatic attack.

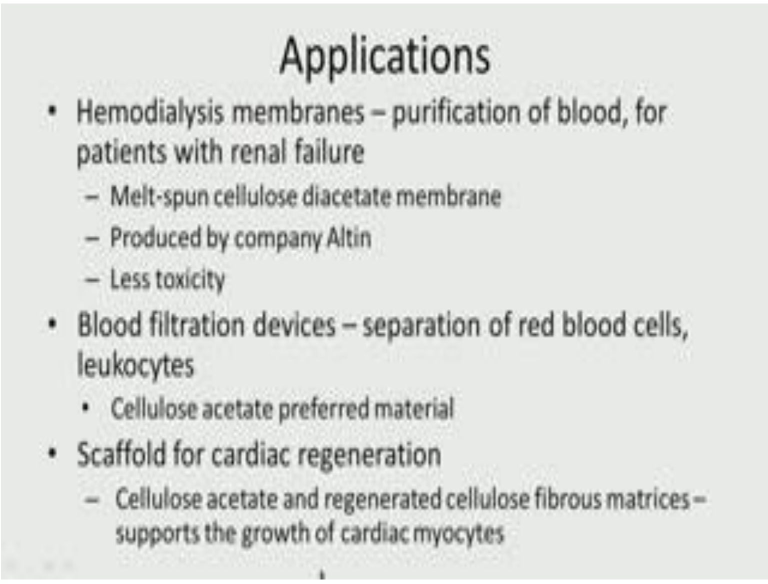
These are linear chains linear chains with 1,000s to 1,500 monomer units. So, we are talking quite a large molecular weight again. So, the degree of linearity and presence of extensive OH group lot of OH groups are present that leads to inter and intramolecular hydrogen bond. So, we can have a lot of inter intramolecular. So, it ends up being a crystal in a parallel arrangement. So, we can have one chain another chain another chain. So, it becomes a crystallized. So, it influences its physical and chemical properties. So, it is widely found its crystalline in nature a lot of OH groups and. So, it forms very good hydrogen bond.

(Refer Slide Time: 07:58)



So, it is poor solubility in common solvent because it is very crystalline poor crease assistance starts if you remember olden days when you put starts to your clothes you have to iron them because this quite very poor crease resistance poor dimensional stability it lack of thermo plasticity high hydrophilicity as you can see large group. So, it is very very water soluble, it does not have antimicrobial properties degradation is also very slow up to 60 weeks. So, what is done is there is a physical chemical modification we can remove some of the OH using acetyl. So, that we reduce the crystallinity and also we can reduce the water solubility there is a thing.

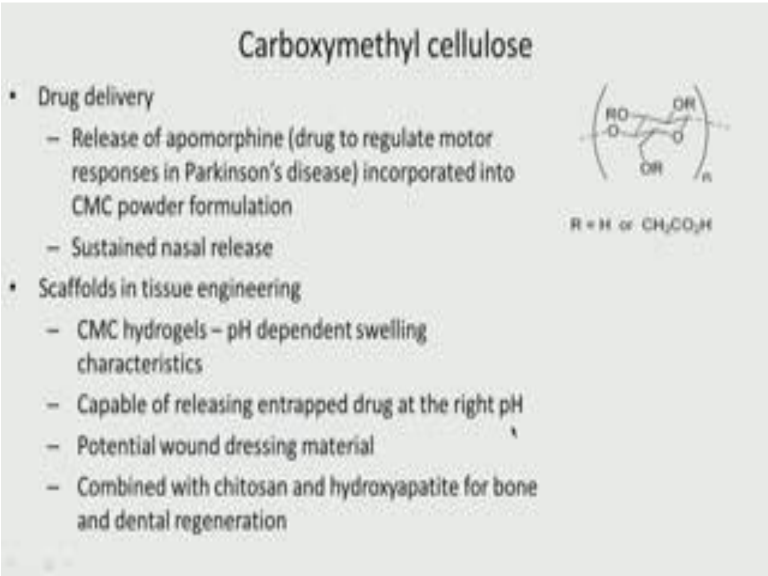
(Refer Slide Time: 08:43)



So, applications hemodialysis membrane they make if you remember those who have a problem with their kidney and it does not function properly removing the urea and creatine; obviously, they have to have this hemodialysis done for purification of the blood for patients of the renal failure. So, cellulose diacetate membranes are used and this is a company called altin which means it is less toxicity.

Blood filtration devices you can separate red blood cells leukocytes size. So, if you are interested in red blood free plasma then we need to filter the blood then cellulose acetate type of membranes are used here scaffolds for cardiac regeneration. So, cellulose acetate and regenerated cellulose fibrous matrices supports the growth of cardiac myocytes. So, we can use them for tissue engineering applications for growing cardiac myocytes. So, these are the applications of this particular product.

(Refer Slide Time: 09:48)

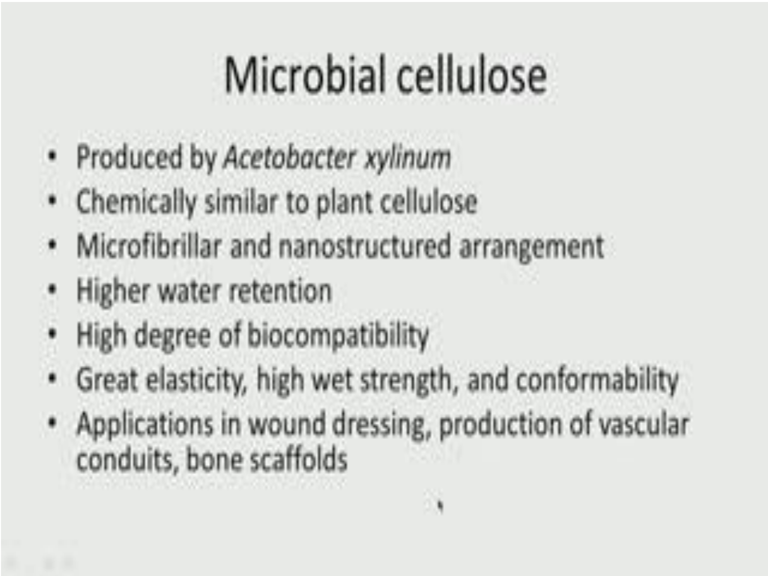


Then comes carboxymethyl cellulose. So, we can convert this if it is H of course, you have the alcohol and so we add the carboxymethyl here then the solubility of it goes down crystallinity also goes down.

Then it can be used for drug delivery release of for example, a drug to regulate motor responses in parkinsons disease when they are incorporated in CMC powder and then we can increase the sustained release of the drug in nasal application and scaffold tissue engineering the called CMC hydrogels they are pH dependent swelling characteristics. So, they can swell and absorb water. So, on the hence they can capture drugs and then you can slowly release at the right pH, the potential wound dressing material and when it is combined with chitosan or hydroxyapatite.

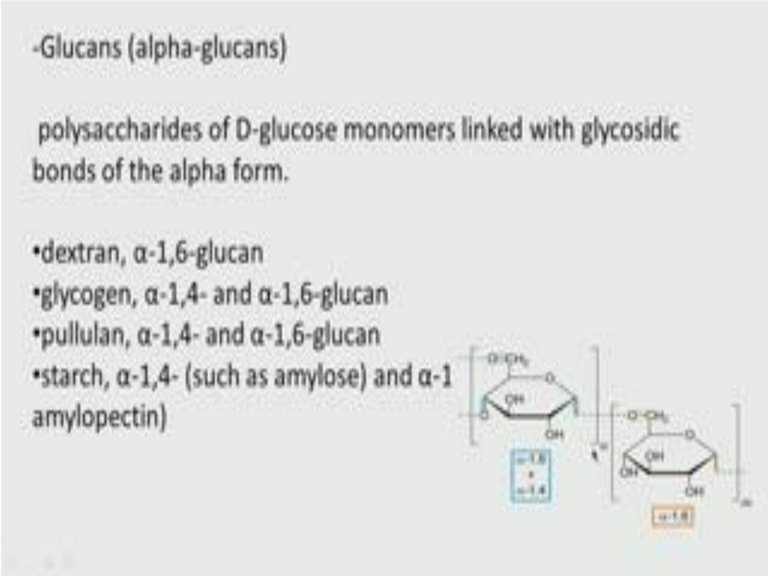
It can also used in bone and dental applications as you know hydroxyapatite use quite a lot in bone chitosan also has very strong. So, it can be used in dental. So, carboxymethyl cellulose will have good biocompatibility. So, they can be combined together.

(Refer Slide Time: 11:03)



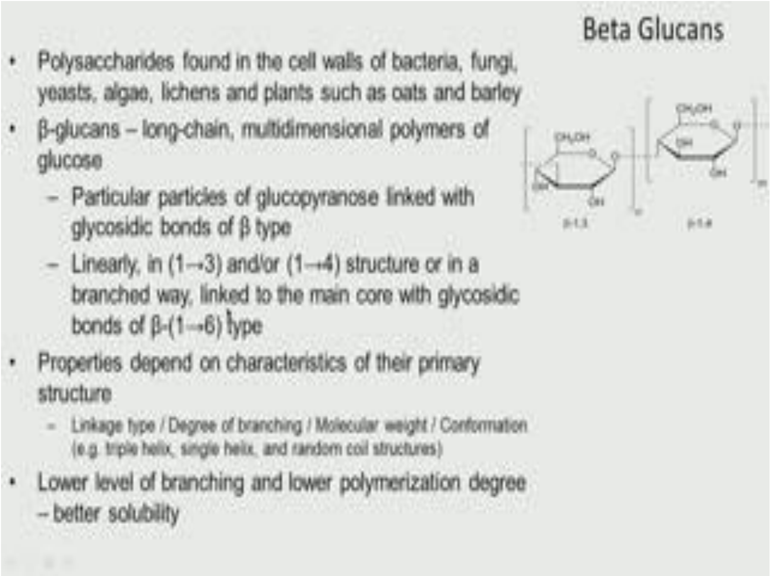
Microbial cellulose these are there the cellulose previous once we saw or plant derived microbes also produce cellulose like acetobacter xylinum and chemically similar to plant cellulose. So, they have a microfibrillar and nanostructured arrangement they can retain water they have very good biocompatibility great elasticity high wet strength confirm. So, it can be used in wound dressing production of vascular conduits bone scaffolds. So, they are to be combined of course, with this with the HA for bone filling and so on actually.

(Refer Slide Time: 11:43)



Then comes glucans and glucans are also polysaccharides either low molecule very low high molecular weight or low molecular weight polysaccharides and. So, alpha glucans and beta glucans are they polysaccharides of D glucose monomers linked through these glycosidic bonds. So, alpha of course, we have the o below like I talked about. So, we have the 1 4 and 1 6 type of arrangement do you see this 1 4 1 6 type of arrangement. So, if you have here and here it is 1 6 if you have here and here it is 1 4 and so, alpha the body a glycosidic bond is below dextran its an alpha 1 6 glucan glycogen it is an alpha 1 4 1 6 pullulan alpha 1 4 and 1 6 starch alpha 1 4 and so all these are alphas and they are called glucans high molecular weight polysaccharides and with do D glucose monomers combined in a linear fashion.

(Refer Slide Time: 13:04)



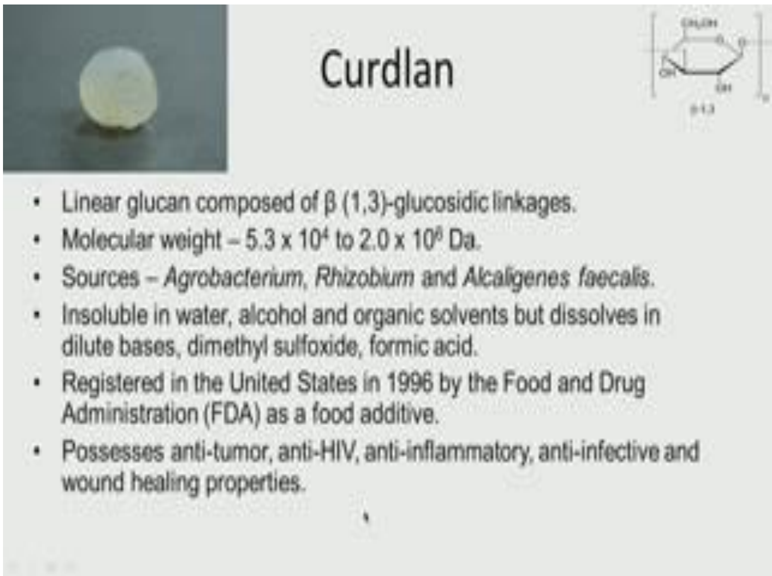
We also have beta glucans the alpha glucans we have the O below in the beta we have the O above they are found in the cell walls of bacteria fungi yeast algae lichen plants such as oats and barley. So, that is the beta. So, we can have beta 1 3 or we can have beta 1 4. So, different types of beta glucans also possible, so, we can see the beta 1 4 and if you have this bond 1, 2, 3, 4, so 1 4 or we can have the beta 1 3; that means, 1, 2, 3. So, different types of combinations are possible these are long chain polymers of glucose they have this beta linkage. So, if it is 1 3 yeah it is going to have be a very linear 1 3 structure you can have 1 4 that can lead to branching you can have beta 1 6 also. So, these linear glucans 1 3 linear glucans can form helical structure they have gelling properties the gelling property can be affected by modifying the temperature. So, quite a lot of applications are already news on this beta glucans.

So, the characteristics; so, it depends on the linkage type; that means, 1 3 or 1 4 or 1 6 degree of branching because when you have 1 6, you can have molecular weight how many chains and linear beta glucans can even be 60 70 kilo Dalton conformational because these linear glucans can form triple helix single helix or random coil. So, they give them the gelling property which changes its temperature lower level of branching a lower polymerization degree its better solubility, but large molecular weight beta glucans are not water soluble they have to be they are soluble only in formic acid or alkali.

(Refer Slide Time: 15:06)

So, examples of beta glucan cellulose beta 1 4 curdlan beta 1 3 laminarin beta 1 3, 1 6 chrysolaminarian beta 1 3 lentinan beta 1 6 1 3 lichenin beta 1 3 1 4 pleuran beta 1 3 and beta 1 6 zymosan beta 1 3. So, we have different types of examples depending upon the glycosidic linkage. So, beta 1 3 curdlan, it is widely found bacteria also produces this.

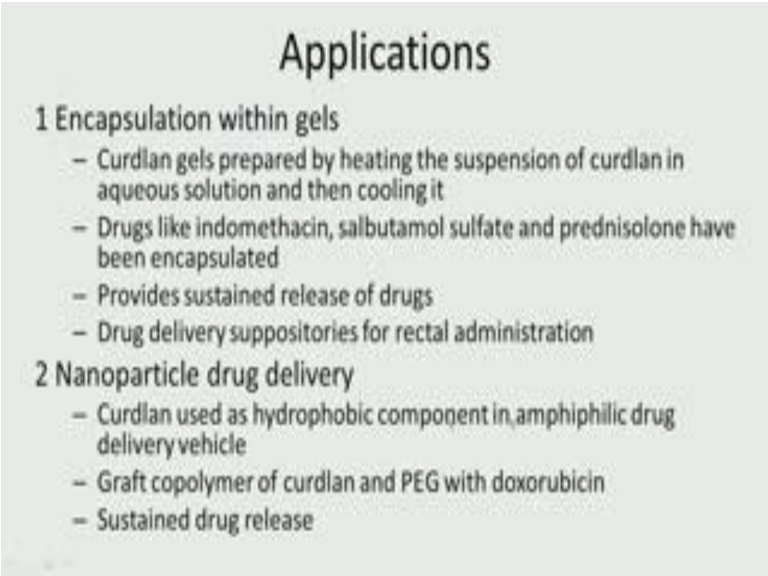
(Refer Slide Time: 15:39)



And it is this is the beta 1 3 glucan beta 1 3, it is also called a curdlan as you can see, it is got jelling properties it forms a triple helix type of structure which forms and breaks depending upon the temperature.

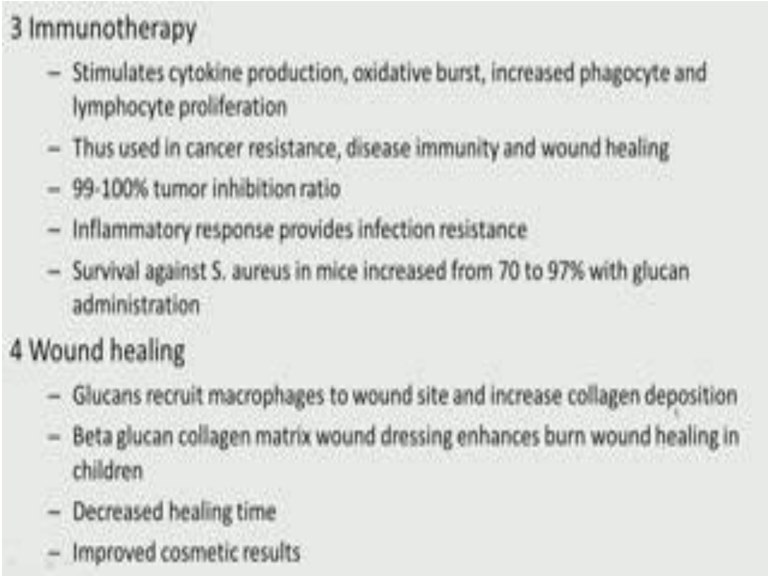
So, these are linear glucan composed of beta 1 3 glycosidic linkage is called glycosidic linkage molecular weight 10 power 4 to 10 power 6 and bacteria produces agrobacterium rhizobium alcaligenes, they all produced maybe about 50, 60, 70 grams per liter. So, it is widely find lot of applications its insoluble in water alcohol and organic solvents, but it dissolves in base valued basis dimethyl sulfoxide DMSO formic acid it is used, it is registered in the USA by in 1996 by the food; FDA as a food additive. So, it is quite used in soup thickening it is for entrapping flavors fragrance a in noodles. So, its widely used in food it possesses anti tumor property anti HIV, anti inflammatory, anti infective wound healing properties of course, it is got very poor and tensile properties, it is got good compressive so; obviously, we cannot use it on its own it needs to be taken with the some other synthetic polymer to look at biomedical applications.

(Refer Slide Time: 17:19)



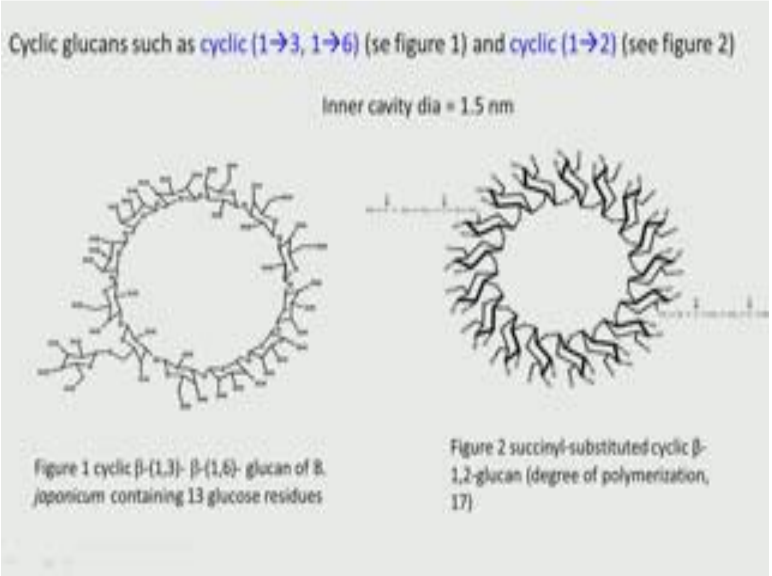
Applications encapsulation within gels and it gets prepared by heating the suspension of curdlan in aqueous solution then cooling it drugs like indomethacin salbutamol sulfate prednisolone have been encapsulated it provides sustained release of drugs it can be also used for drug delivery through rectal administration suppositories, we can also make nanoparticles of this of curdlan because its hydrophobic component in amphiphilic drug delivery vehicle we can graft polymer copolymer curdlan with PEG and then put in a drug like a doxorubicin which can lead to sustained drug release that is another example.

(Refer Slide Time: 18:05).



Immunotherapy because these beta glucan the linear beta glucan and the beta 1 3 linkage gives them the immunomodulatory properties. So, it seems it stimulate cytokine production oxidative burst increased phagocyte and lymphocyte proliferation. So, it can be looked at cancer resistance disease immunity wound healing and it also been reported for tumor inhibition ratio, it also gives good inflammatory response and provides infection resistance and the survival against staff aureus in mice increased from 70 to 97 percent with glucan administration the beta 1 3 gives immunomodulatory properties and hence and these are possible applications of this beta glucan or curdlan wound healing they can recruit macrophages to wound site and increase collagen deposition. So, we can combine beta glucan collagen matrix as wound dressing especially for burn wound healing in children decreased healing time improved cosmetic results.

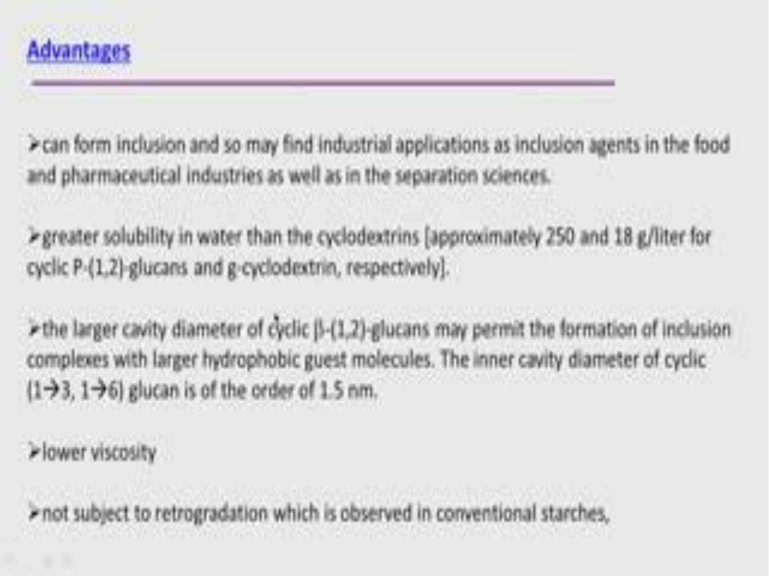
(Refer Slide Time: 19:10)



Then comes cyclic glucans and beta glucans the linear beta glucans its mentioned is about 62, it is almost 10 power 5 Dalton molecular weight and it is not water soluble it is been approved by FDA and this cyclic glucans on the other hand or small molecular weight biopolymers they have a cyclic structure like this they have cyclic 1 3 1 6 of cyclic 1 2, they are very hydrophilic they are water soluble, but the inner cavity is hydrophobic. So, we can put in hydrophobic drugs very conveniently the inner cavity diameter is about 1.5 nanometer this is a picture of 1 3 1 6 cyclic beta glucan produced by japonicum, it contains 13 glucose units and this is a 1 2 beta cyclic glucan. So, the degree of polymerization is 17; that means, there are 17 glucans in it.

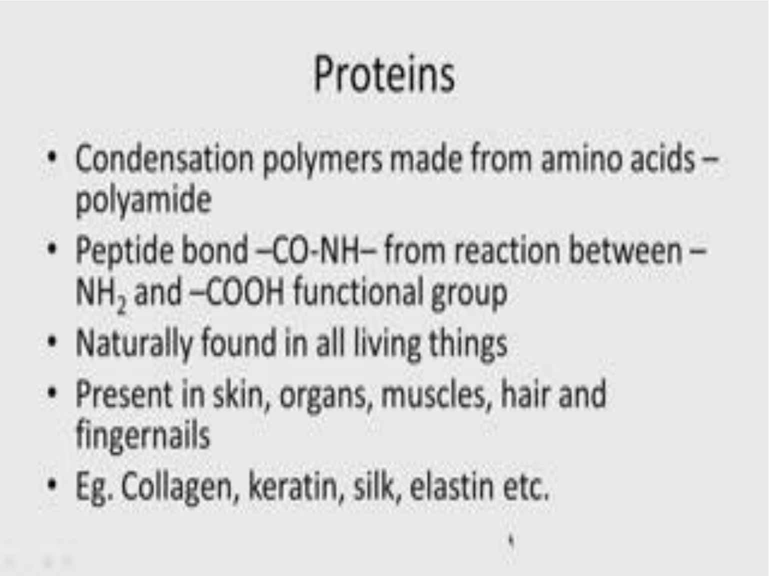
So, these 2 are common cyclic 1 3 1 6 cyclic 1 2 they have big in a cavity diameter. So, we can even encapsulate large drugs in to it that is the advantage also.

(Refer Slide Time: 20:26)



What are the advantages they can form inclusion? So, may find industrial applications in food pharmaceutical industries and there are some literature where they have been used for chiral separation of biomolecules small molecules using the advantage of the it is like the cavity thats present in the cyclic beta glucan its got greater water solubility than cyclodextrins you are talking in terms of 250 grams per liter soluble in water when compared to eighteen grams of cyclodextrin that is the advantages large cavity diameter of cyclic beta 1 glucan may permit the formation of inclusion complex because the inner cavity diameter say for example, of 1 3 1 6 is about 1.5 nanometer, it is got lower viscosity it is not subject to retro gradation; that means, degradation which is observed in conventional structures and when it is kept for over a long period of time. So, they do not degrade. So, they may have better and shelf life.

(Refer Slide Time: 21:32)

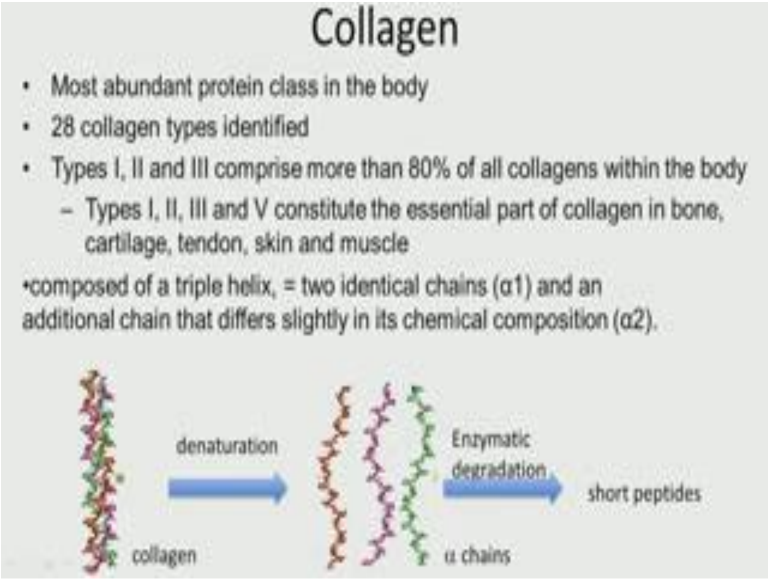


Now, comes proteins we looked at the polysaccharides; polysaccharides are those which have sugar in them and arranged different types of sugars arranged in alpha or beta connected with the 1 2, 1 3, 1 4, 1 6 type of leakages. So, different types of sugars and we have amino groups present then acetyl deacetyled and so on. Now comes protein; that means, that they have an amide bond they are produced by condensation of amino acids that is polyamide.

So, they will have all of these will have an amide bond; that means, a peptide bond c o n h because of the reaction between NH 2 and COOH that is how you form, this CO NH group they are called amide bond or peptide bond and. So, there are proteins which are naturally occurring different types of proteins we will look at them they are found in living things present in skin organs muscles hair and fingernails so; obviously, they can find applications in tissue engineering they can find application in wound dressing and so on.

So actually for example collision it is widely found in our body keratin silk elastin. So, all of them have very good biocompatibility bio recognition properties.

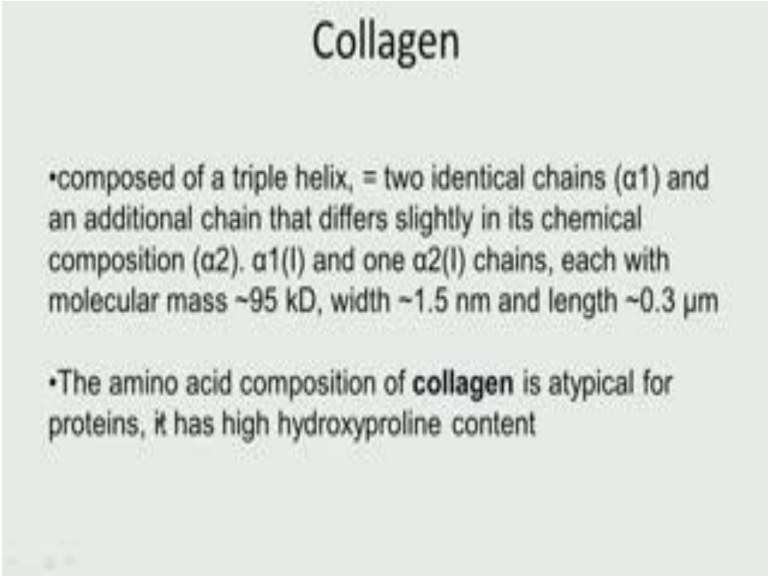
(Refer Slide Time: 23:07)



For example collagen; so, most abundantly found protein in the body there are 28 collagen types type 1, 2 and 3 comprise of 80 percent of all collagens within the body because the 1, 2, 3 and 5 constitute the essential part of collagen in bone cartilage tendon skin and muscle.

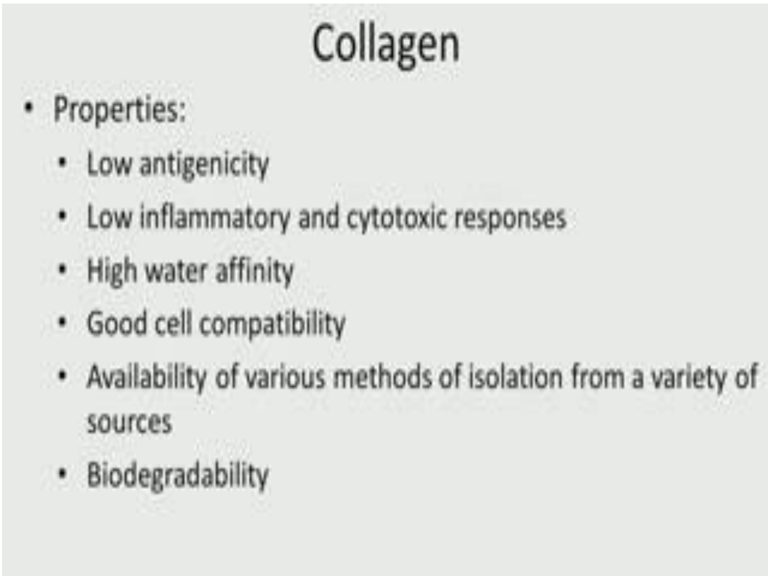
It is composed of triple helix like this you know collagen has a triple helix. So, they have 2 identical alpha 1, these are called and there is something called an alpha 2, there is a slight difference in their chemical composition they are connected as a triple helix they get denatured if you denature you will get them and if you have the enzymatic degradation of you will get short peptide small, small, small, small peptide like this actually collagen. So, the structure of collagen was originally discovered as you know by an Indian scientist G Ramachandran; Professor G Ramachandran and found out this that it forms a triple helix it is composed of a triple helix 2 identical chains alpha 1 and then one middle one that is called alpha 2.

(Refer Slide Time: 24:15)



So, the alpha 1 has a molecular mass weight of 95 kilo Dalton width of 1.5 nanometers and the 0.3 micron. So, the composition of collagen is a typical for proteins. So, it is got very highly hydroxyproline content. So, it caused very high hydroxyproline content.

(Refer Slide Time: 24:51)



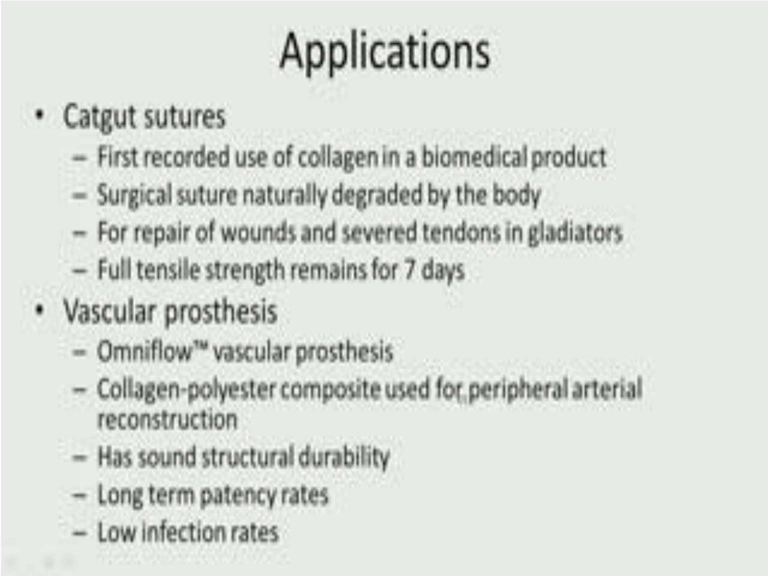
So, what are the properties is got low antigenicity low inflammatory and cytotoxic responses, it is got a very high water affinity got good silk compatibility and availability of various methods for isolating some variety of sources biodegradable it is found the collagen is found in human bones and tissues in abundant so; obviously, when we make a material with collagen the system the human body and human system will not consider it as a foreign body. So, hence there is a lot of research being done on collagen as a possible biomaterial in the tissue engineering area cartilage design in filling in orthopedic area and so on actually.

(Refer Slide Time: 25:41)

So, advantages are available in abundance and easily purified from living organism non antigenic biodegradable bioresorbable non toxic biocompatible synergic with bioactive components. So, it is got good tensile strength and minimal minimal expressibility hemostatic it promotes by blood coagulation and disadvantages pure type own collagen is very expensive. So, variability of isolated collagen cross linked there are a lot of variations crosslink density can change fiber size can change there could be impurities and because it is highly hydrophilic it could start swelling and hence if we are encapsulated any drugs it is the rapid released. So, variability in enzymatic degradation rate as compared with hydrolytic degradation.

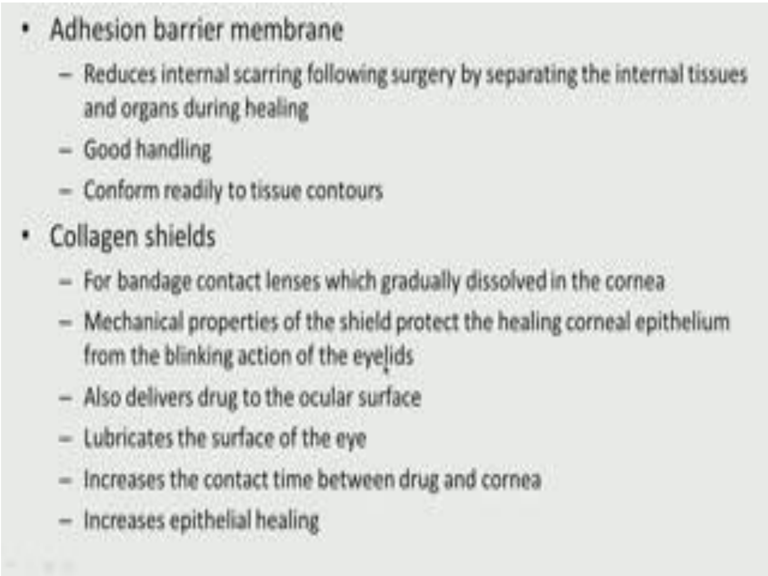
Complex handling properties there are a lot of side effects for example, if I isolate a collage collagen from a bovine and. So, we could have some toxicity bovine spongiform encephalopathy and mineralization all these; a foot and mouth disease which can get transmitted from these animals.

(Refer Slide Time: 27:02)



So, the scare of that is very very serious. So, it can be used for many things already its catgut sutures first recorded use of collagen in a biomedical product surgical suture. So, it degrades by the body repair of wounds and severed tendons in gladiators got full tensile strength which remains for 7 days then vascular prosthesis prothesis. So, already there is a product omniflow which is used for vascular prosthesis. So, collagen polyester composites used for peripheral arterial reconstruction a sound structural durability long term patency rates low infection rates.

(Refer Slide Time: 27:46)



Addition barrier membrane; it reduces internal scarring following surgery by separating the internal tissues and organs during healing they have got good handling property it confirms readily tissue contours then shields for bandage contact lenses which gradually dissolved in the cornea. So, the mechanical properties of shield protect the healing corneal epithelium from the blinking actions eyelids it also delivers drug to the ocular surface lubricates the surface of the eye increases the contact time between drug and cornea increases epithelial healing. So, lot of advantages of collagen. So, as I said there are already some products in the market and there is a lot of research being done on the use of collagen into biomedical applications we will continue further on these proteins based natural biomaterials in the next class also.

Thank you very much for your time.