Medical Biomaterials
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Lecture – 35
Hydrogels

Hello everyone, welcome to the course on medical biomaterials we will continue on the topic of hydrogels, I just introduced the topic yesterday in the previous class hydrogels are as the name implies jelly type of polymeric material it could be a natural or it could be synthetic and it takes lot of water in it that is why they are called hydrogels.

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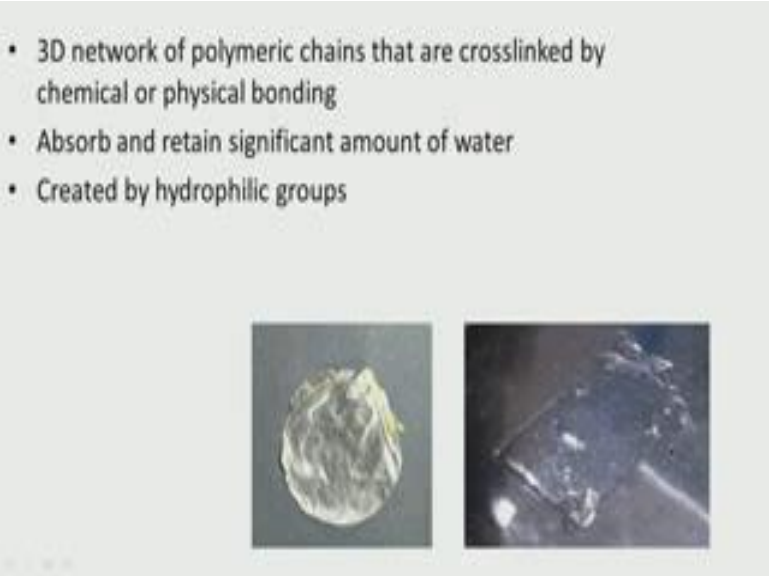

For example if you look at this picture the one here is dry material dry polymeric material, but when it takes up water as you can see in this other picture it is swells a lot and that is why they get the name of hydrogels. So, it is a 3D network of polymeric chains that are cross linked by chemical or physical bonding there are bonds of chemical nature or physical could be like not bonded interactions and. So, on actually and they absorb retain large amount of water and there are a lot of hydrophilic groups there are even groups which has negatively charged.

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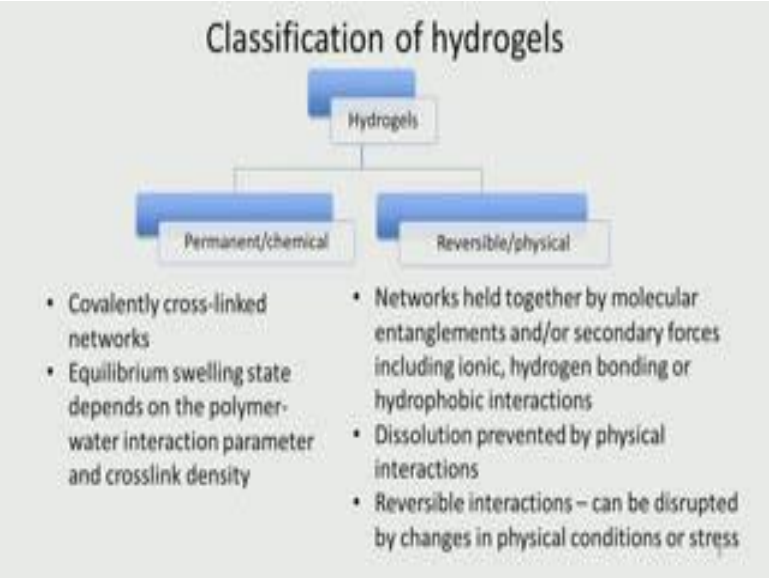

So, they can take up cautions and so on actually. So, the classification of hydrogels, we have permanent chemical bonded or reversible physical bonded; that means, when there is a physical bonding its reversible and; that means, the material can be hydrogel by adding water or it can it can give up all the water or it could be a permanent the chemical bonding. So, chemical bonding could be covalent cross linking equilibrium swelling depends on the polymer water interaction and cross link density whereas, physical the networks are made up of molecular entanglement or secondary forces like ionic forces hydrogen bond forces hydrophobic interactions and. So, on and the dissolution is prevented because of this and these are all very reversible. So, when I change the physical conditions or stress they may come back at the dry state.

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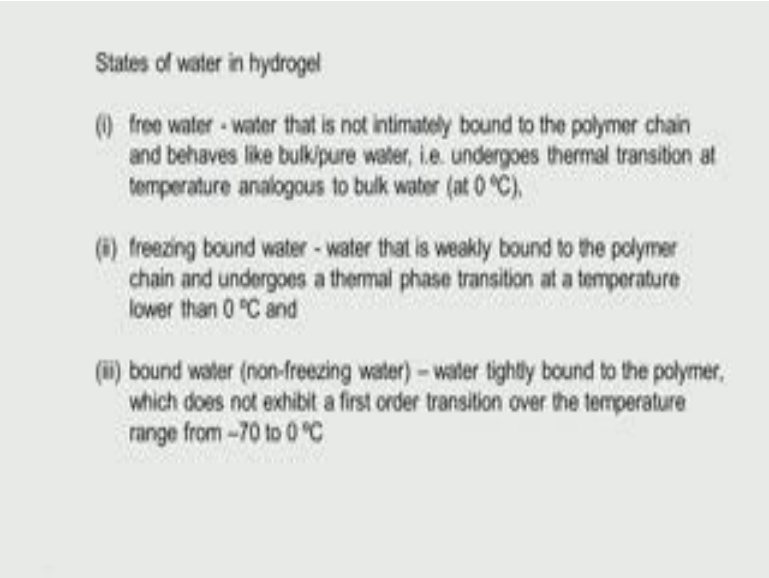

So, there are 3 types of water in hydrogel, one is called the free water that is the water which is exactly like the water that is present in the bulk that is like a pure water. So, it will get frozen when the temperature is lowered may be at around 0 degree centigrade it exactly behaves like the water present in the bulk then we have freezing bound water that is the water which is weakly bound to the polymer chain and this also undergoes thermal phase changes; that means, this also can get frozen and this also can become liquid, but generally it is and below 0 degree centigrade then will have the bound water non freezing time; that means, the water is strongly tightly bound to the polymer. So, it will not freeze and become liquid like these freezing bound water or free water. So, the phase changes may happen much much lower, you will not see a phase change also for all a new. So, 3 types of water present in hydrogel. So, materials which absorb water does not mean it is a hydrogel, but materials which absorb water where the water is in these 3 different forms we can call this a hydrogel.

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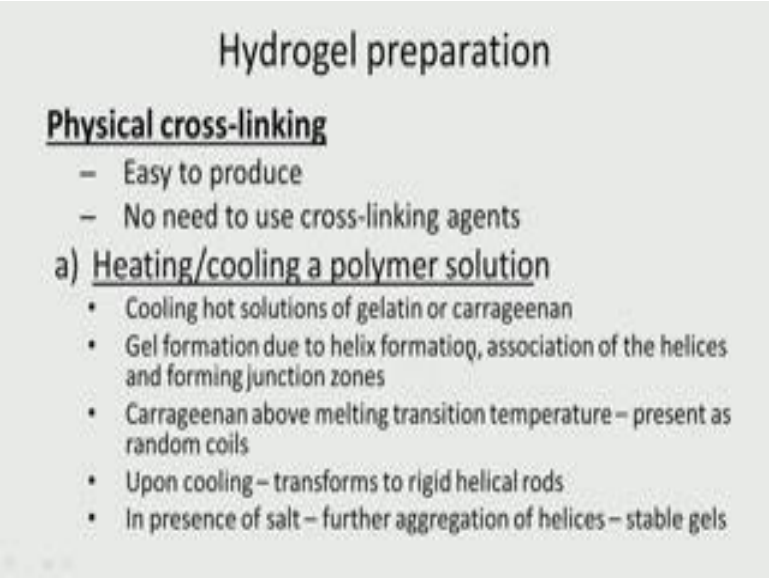

Now, how do you prepare this hydrogen we can do it by physical cross linking or through chemical process like I said you know physical? So, easy to produce no need to use cross linking agents like glutaraldehyde or some other small molecules. So, one approach heating cooling a polymer solution, when I cool hot solutions of gelatin or carrageenan, it forms a gel due to the helix formation; that means, as the temperature is lower these material forms helical structure even linear glucans and the temperature is lowered they form helical structures now these helices have junctions and crevices where the water can be tracked.

So, carrageenan about this melting transition temperature they are random coil, but when you keep reducing the temperature they form this helical structure. So, these are rigid helical rods. So, they form hydrogels. So, when you have salts present of course, they can aggregate and they form very stable gels because the salts will have both cations and anions so, they form very strong bonding.

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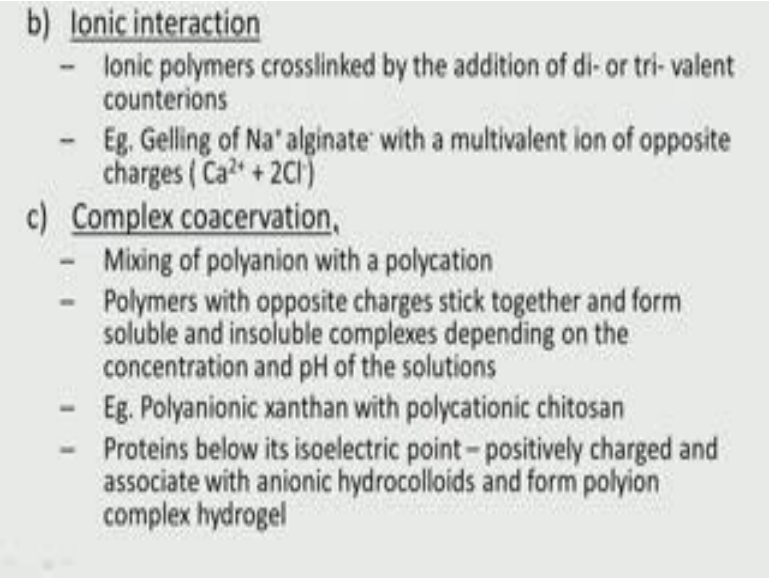

Ionic interactions; so ionic polymers cross linked by the addition of di-or tri-valent counterions. So, I could add calcium 2 plus for example. So, if you take sodium alginate like the name implies sodium and alginate. So, we can add calcium to that then when we add this type of multivalent and cations it forms a gel because calcium has 2 charges a 2 plus charge.

So, it can connect 2 different alginate change another one is complex coacervation that is coacervation means we have both anion and cation or 2 groups of molecules of different charges coming together. So, mixing of polyanion and polycation polymers with opposite charges stick together and form soluble and insoluble complexes, depending upon the concentration on the pH like polyanionic xanthine with polycationic chitosan. So, they have this complex coacervation because of the positive the negative charge proteins below its isoelectric point. So, we have positively charged and associate with anionic hydrocolloids and form polyion complex hydrogel. So, so you are creating this positive charge and proteins below the isoelectric points.

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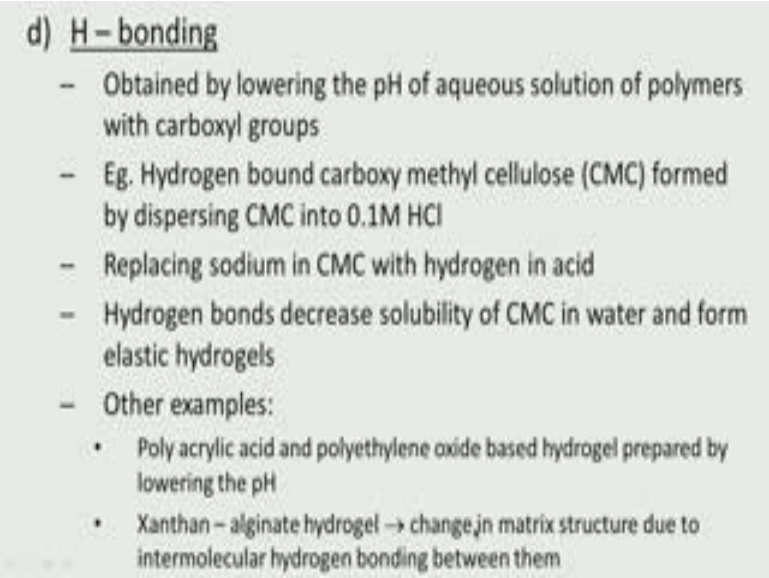

So, I can add anionic hydrocolloids. So, that they form complex hydrogel these are all ionic type of hydrogen bonding obtained by lowering the pH of aqueous solution of polymers with carboxyl group hydrogen bond carboxy methyl cellulose formed by dispersing CMC and HCL. So, we have both replacing sodium in c m c with hydrogen in acid. So, when we add sodium gets replaced by H. So, it can form hydrogen bond hydrogen bonds decrease the solubility of CHC in water. So, they form elastic hydrogels.

Other examples we have a poly acrylic acid and poly ethylene oxide based hydrogel prepared by lowering the pH xanthan alginate hydrogel change in matrix structure due to intermolecular hydrogen bonding between them. So, all these are examples where there is hydrogen bond plays a very very important role in creating this particular hydrogel system then maturation or heat induced aggregation.

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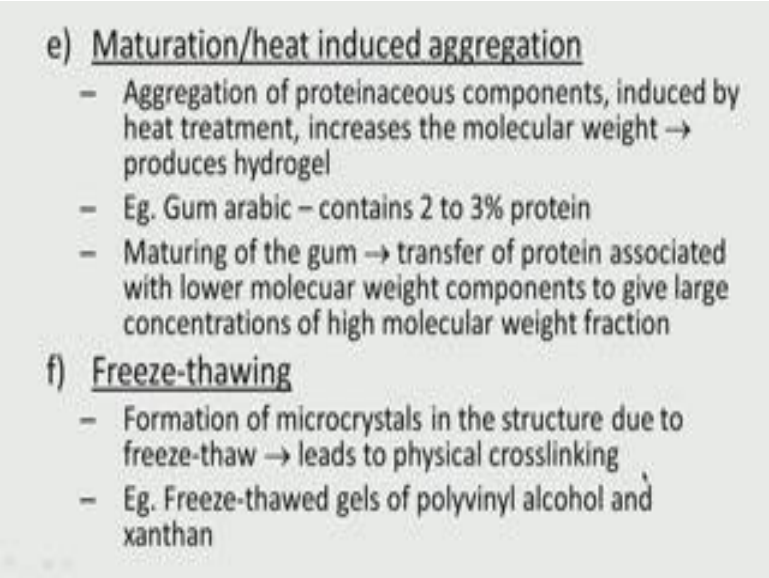

So, aggregation of proteinaceous components induced by heat treatment, so when you have heat treatment increases the molecular weight so that produces hydrogel. So, gum arabic containing 2 to 3 percent protein. So, maturation of the gum transfer of protein associated with lower molecular weight components to give large concentrations of high molecular weight. So, these are all heat induced freeze thawing. So, when we freeze and thaw formation of micro crystal in the structure due to the freeze thaw leads to physical cross linking. So, please freeze thawed gels of polyvinyl alcohol and xanthan. So, when I reduce the temperature it forms micro crystals and that leads to physical cross linking all these are physical based method.

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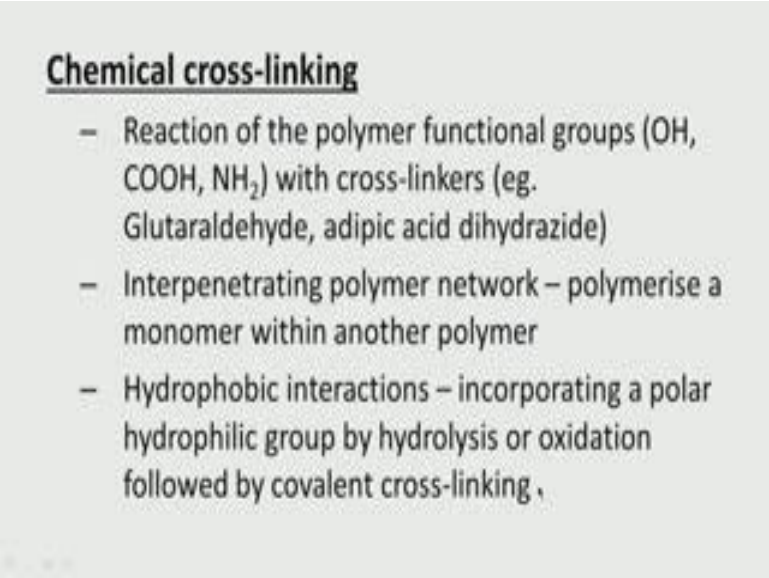

Now, we come to chemical base. So, physical base method like I said we have heating cooling a polymer solution.

Then we have the ionic interaction adding a di or tri valent ions complex coacervation formation of hydrogen bonds then maturation heat induced aggregation and then freeze thawing these are all physical methods now let us go look at chemical cross linking. So, there we are create we are having a reaction. So, there is a bond formation. So, that is the chemical cross linking. So, reaction of the polymer functional groups like OH, COOH, NH2 with cross linkers like glutaraldehyde, adipic acid, dihydrazide like that you know. So, we add all these. So, they react with the functional groups in polymer because many polymer contains select PVA contains OH if you are looking at acrylic acid contains COOH and then if you look at sugar some sugars they have n h amine amide so on.

So, they all cross link using glutaraldehyde glutaraldehyde is very commonly used interpenetrating polymer network polymer is a monomer within a mono another monomer. So, we have a monomer we have another monomer then we sort of interpenetrating polymer networks. So, that is a chemical cross linking hydrophobic interaction incorporating a polar hydrophilic group by hydrolysis or oxidation followed by a covalent cross linking. So, I will incorporate a polar hydrophilic group and then we oxidize and then we do a covalent cross linking that is another type of approach.

So, we create in a polymer hydrophilic group by having a polar hydrophilic group then we hydrolyze or oxidized and then we cross linked the system.

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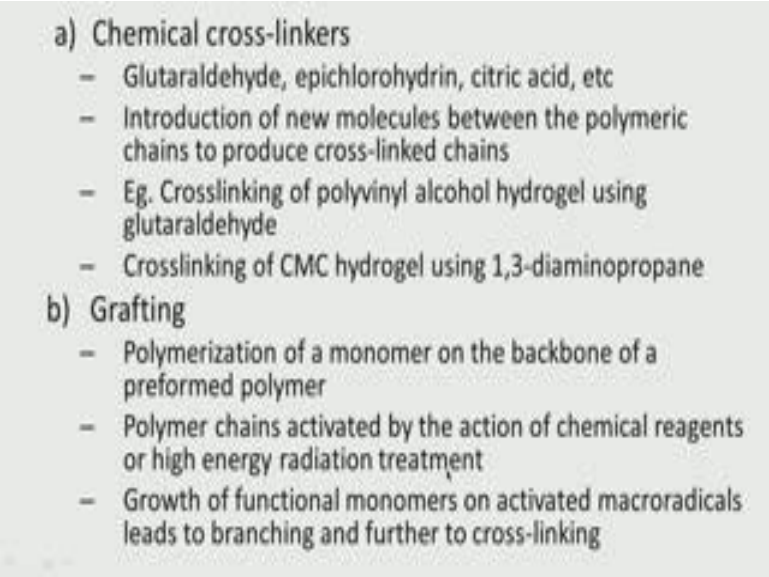

So, chemical cross linkers further what do we use you use glutaraldehyde epichlorohydrin these are all very commonly used citric acid introduction of new molecules between the polymeric chains to produce the cross linked. So, if we have 2 chains in between these 2 chains we are putting in epichlorohydrin or glutaraldehyde now for example, cross linking of PVA hydrogel using glutaraldehyde cross linking of CMC using 1, 3-diaminopropane. So, all these are small molecules which are in between 2 chains then come grafting that is polymerization of a man of monomer and the backbone of a preformed polymer.

So, we have a polymer then we put in another monomer and start polymerizing polymer chains activated by the action of chemical reagents or high energy radiation. So, we activate them by putting in some radiation or we add some high reactive functional groups growth of functional monomers on activated macro radicals leads to branching and further cross linking. So, we already have a chain long chain we create radicals and then we create branching and then cross linking that is called grafting method.

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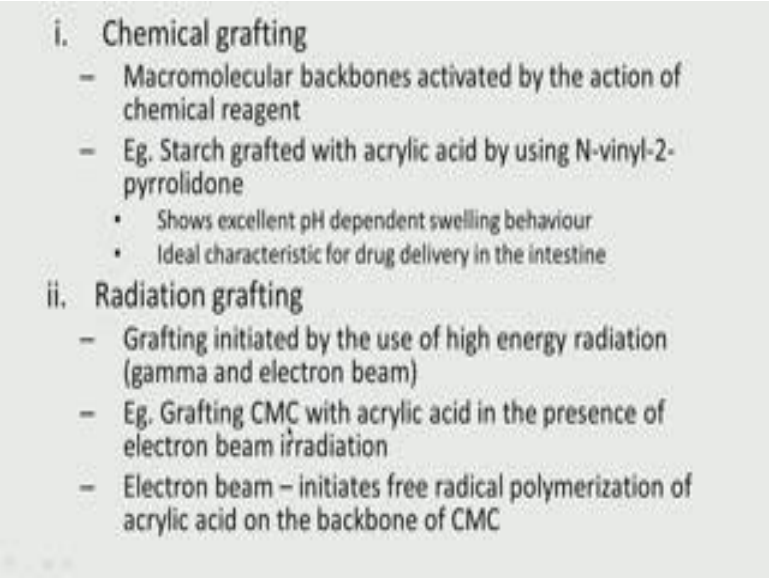

This grafting has a chemical grafting radiation grafting. So, in chemical grafting what do we do you have a macromolecular backbone this activated by the action of chemical reagent. So, we have starch grafted with acrylic acid by using N vinyl 2 pyrrolidone. So, we have starch backbone then we put in acrylic acid using this particular chemical. So, it shows excellent pH dependent swelling behavior ideal characteristic for drug delivery in the intestine otherwise pure starch is not very very suitable other one is radiation grafting; that means, we initiate the grafting using high energy radiation like gamma or electron. So, when this bombards the backbone they create radicals which are ready for chemical modification grafting CMC with acrylic acid in the presence of electron beam. So, the electron beam what does it do it initiates free radical polymerization of this acrylic acid and CMC. So, that is called radiation grafting. So, we have chemical grafting; that means, chemicals modify the backbone and then it add other functional groups or radiation that creates functional groups or radicals. So, we can add another monomer and then polymerize it further. So, we have radiation cross linking that is the third approach.

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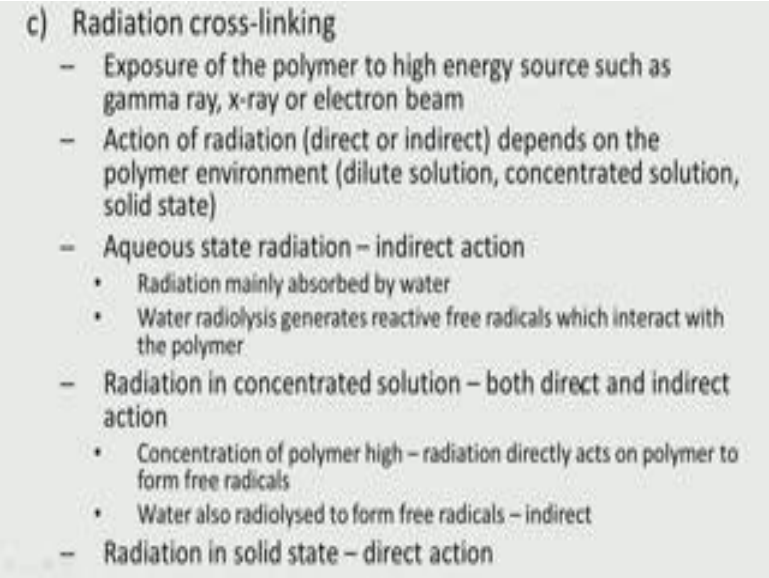

So, here exposure of the polymer to high energy source such as gamma ray x ray electron beam and then this leads to direct or indirect depends on the polymer environment solution concentration solid state and so on.

So, what do we do another approach we do the radiation, but we immerse the polymer in aqueous. So, the radiation mainly absorbed by water; water radiolysis generates reactive free radicals which interacts with the polymer. So, you are actually radiating the water which generates free radicals which in turn generates free radicals on the polymer radiation concentrated solution these are different approaches of this radiation both direct and indirect concentration of polymer high radiation directly acts on the polymer to form free radicals what is also radiolysed to form free radicals these are indirect method this is indirect method this is direct method these are all based on radiation cross linking.

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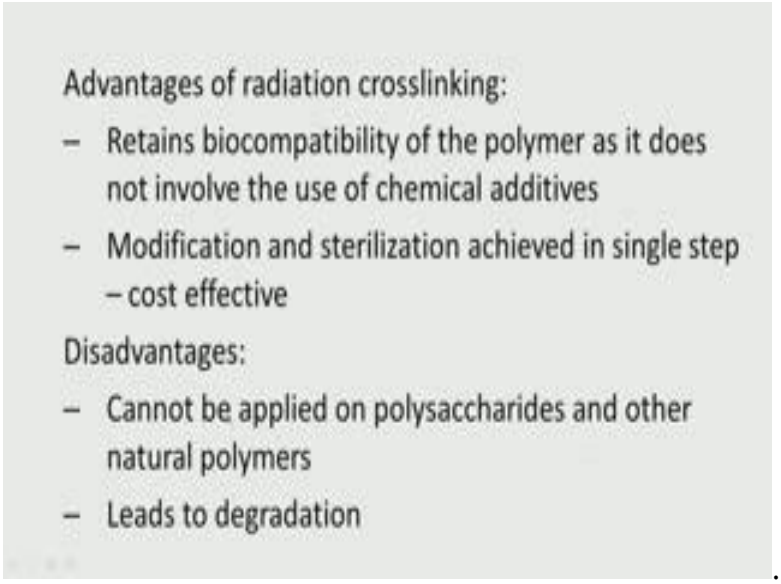

So, what are the advantages it retains biocompatibility of the polymer as it does not involve the use of chemical additive. So, if you are using a chemical cross linker the polymer is getting modified sometimes their functional groups get modified reactivity may modify hydrophilicity may modify the surface energy may get modified and the advantage of radiation is we are achieve modification as well as sterilization. So, it is very good cost effective disadvantages cannot be applied on polysaccharides another natural polymers because the polysaccharides or other biopolymers will completely get disintegrated. So, it leads to degradation. So, that is the big problem about using something like radiation grafting.

So we have chemical we have different approaches right we talked about chemicals we talked about radiation and so on actually.

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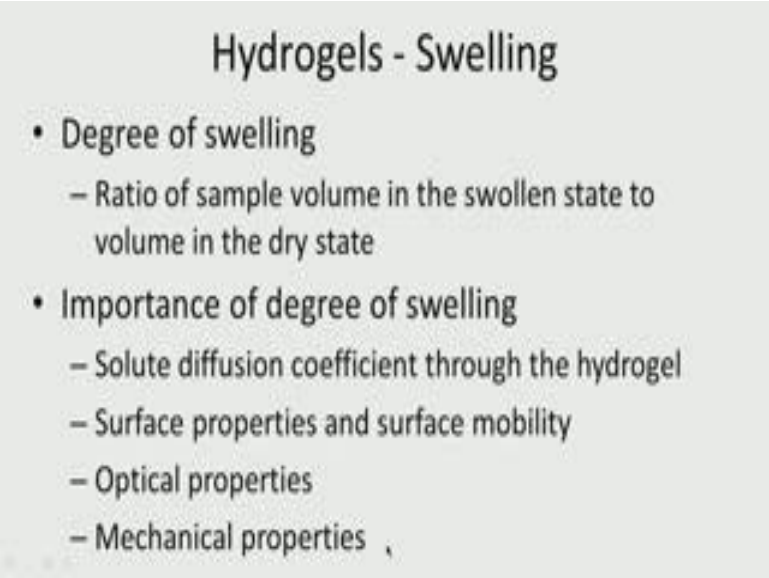

Now, these hydrogels one of the most important thing is they swell they take lot of water. So, it can be used and for skin grafting open wound treatment. So, swelling is a very very important part of this hydrogel. So, we can even put in a drug antibiotics or anti-inflammatory molecules. So, that when it releases it helps in the treatment of the bone wounds or scars and so on. So, that is degree of swelling ratio of the sample volume this swollen state to volume in the dry state. So, we can look at volume or weight and then see how much change happens when as a function of time and it is put in to the; and it is put in to water. So, it helps importance of degree of swelling. So, your diffusion coefficient surface properties and surface mobility optical properties mechanical properties although these hydrogels cannot be used in mechanical and environment force related environment because they have very poor strength still handling of the hydrogel is very very important. So, it should be able to sustain that sort of forces ok the diffusion is also very important because when we are talking about a drug uptake and drug release the diffusion of the drugs from the hydrogel plays a very important role.

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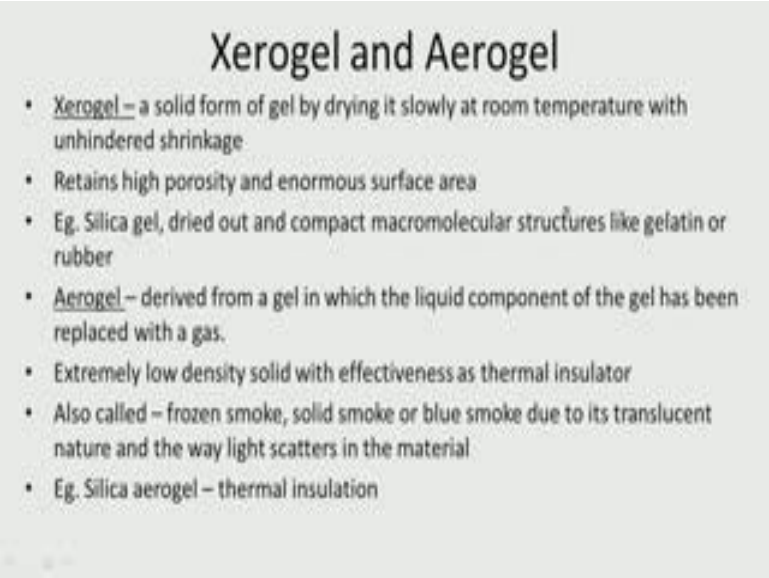

There are something called Xerogel; Xerogel and Aerogel 2 types of hydrogel at the xerogel and aerogel this is a solid xerogel is a solid form of gel by drying it slowly at room temperatures with unhindered shrinking. So, we slowly try to dry the gel without any shrinkage then that is called xerogel it retains high porosity because you are not allowing it to shrink and it is also covered very good the surface area like silica gel dried out and compact macromolecular structures like gelatin or rubber they all come under that whereas, aerogel this is derived from a gel in which the liquid component of the gel has been replaced with a gas that is why it is called aero no air.

So, it can be any gas it can be air or it can be even some gas that is called the aerogel it is very low density solid because we have lot of pours filled with them water it can be used as a thermal insulator they are also called frozen smoke solid smoke or blue smoke due to its translucent nature and the way light scatters in the material like silica aerogel they are very good at thermal insulation. So, we have 2 types of gels xerogel we are allowing it to dry without unhindered shrinkage. So, it has got very high porosity and enormous surface area aerogel, we have air or any gas molecules inside those voids. So, they have very low and density and very light weight and they are very good thermal insulators.

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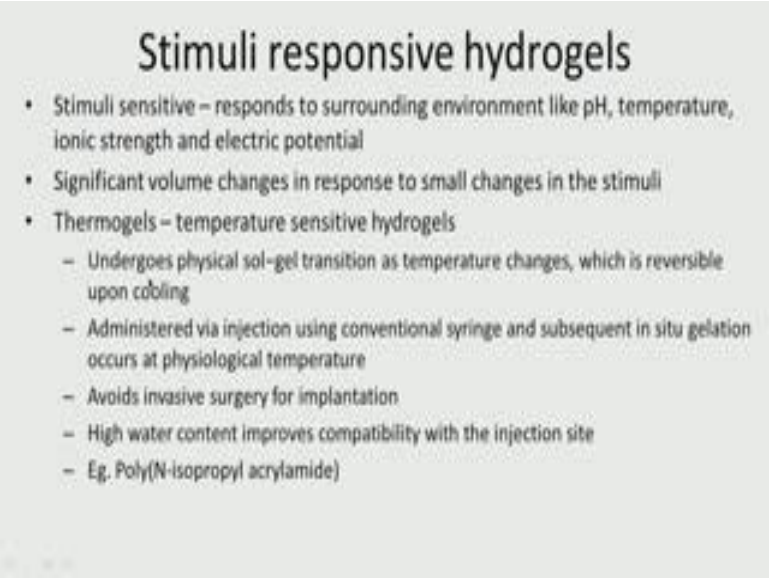

Then stimuli responsive hydrogels because hydrogels if they can respond based on pH or temperature or any other environment it may be very useful if you want to deliver drugs. So, stimuli sensitive response to surrounding environment like pH temperature ionic strength and electric potential. So, those such gels are very very good to have. So, significant volume changes in response to small changes in the stimuli. So, small change in pH and then we expect the volume change to be very large thermo gels they are temperature sensitive.

Hydrogels; that means, when there is a change in temperature these hydrogels start releasing say drug or moisture. So, physical sol gel transition as temperature changes which is reversible upon cooling. So, this can be administered by injection using conventional syringe and subsequent in insitu gelation occurs at physiological temperature. So, we can inject a cold and gel and inside the body it can become hydrogel. So, it avoids invasive surgery for implantation high water content improves compatibility with injection within the injection site. So, we can target like poly n isopropyl acrylamide, this is a hydrogel which temperature sensitive. So, this is a thermo sensitive gel.

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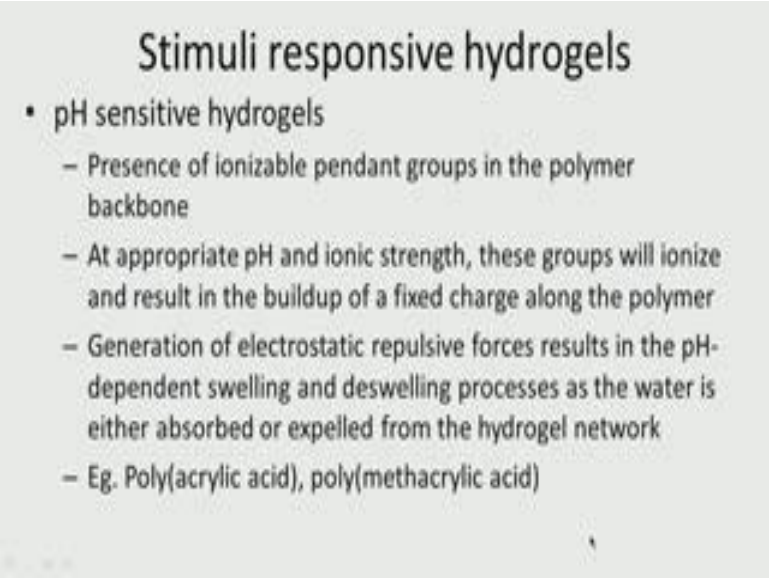

P h sensitive gels pressure of ionizable pendent groups in the polymer backbone. So, we have a pendent group in the polymer. So, at certain pH they get ionized. So, next the pH sensitive hydrogels at appropriate pH ionic strength these groups will ionize and the result in the build-up of a fixed charge along the polymer and this electrostatic repulsive forces results in the pH dependent swelling and deswelling process as the water is either absorbed or expelled from the hydrogel network. So, we can have for example, at tumor size the pH is acidic. So, the hydrogel may be able to release at that particular condition drugs that has been encapsulated or water or any other chemical that has been encapsulated poly acrylic acid poly methacrylic all these are pH sensitive.

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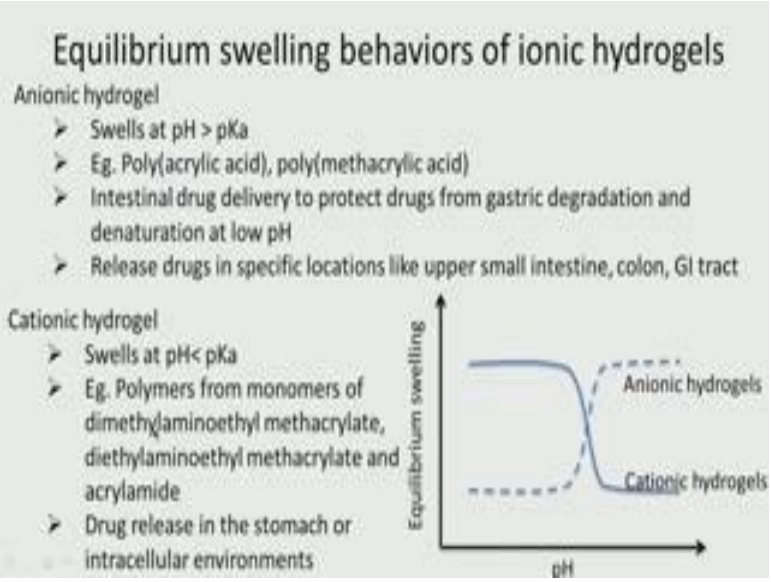

So, equilibrium swelling behavior of ionic hydrogels. So, we have these ionic hydrogels now what happens if you take a cationic hydrogel. So, as the pH is increased. So, equilibrium swelling is very high at low pH because their cationic at acidic pH when it comes down dramatically in the it goes to basic whereas, anionic hydrogels they have very low equilibrium swelling whereas, as becomes basic this start swelling like no as shown.

Sure these are the cationic hydrogels and these are the anionic hydrogels. So, anionic hydrogels this one swells at pH greater than PKA that is the side like poly acrylic acid poly methacrylic acid intestinal drug delivery to protect drugs from gastric degradation and denaturation at low pH. So, as you know stomach or gastric pH is very very low. So, we can have hydrogels like this. So, it prevents the denaturation. So, it releases drugs in specific location like upper small intestine for example, when it goes to the small intestine, the pH starts going up stomach maybe 2 in intestine upper ligand is my go to 4.

So, it may release the drug or colon not GI tract and so on actually. So, we can control based on the pH where it needs to the cationic hydrogel pH less than PKA here polymers from monomers of dimethylaminoethyl methacrylate d m d m e a m diethylaminoethyl methacrylate and acrylamide. So, drug release in the stomach or intra cellular environment so; that means, here in the stomach you want it to be released that is at very low p h. So, these cationic hydrogels are very very good anionic hydrogels are very good

if you are talking about intestine region or colon region. So, depending upon the pH the anionic hydrogels will release at higher pH and cationic hydrogels will release at lower pH because of the equilibrium swelling.

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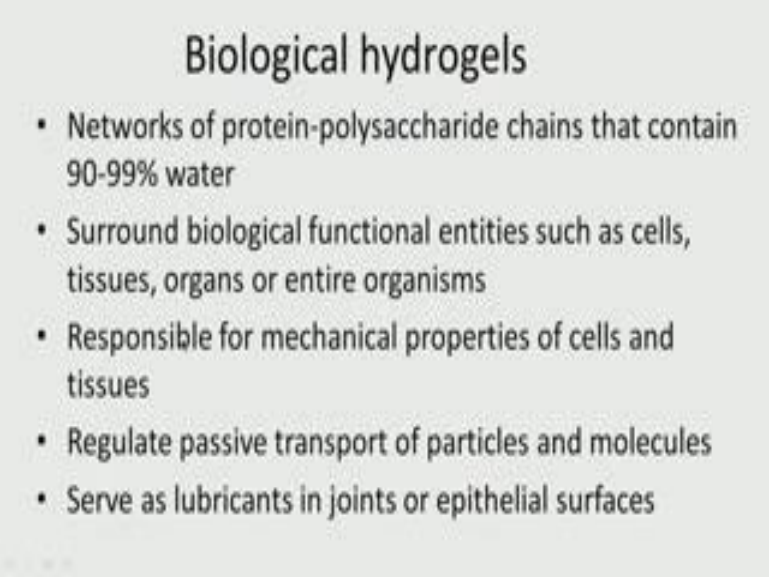

So, next biological hydrogels these are networks of protein polysaccharide chains that contain 90 to 99 percent of water cells tissues organs or entire organisms. So, there can be called as biological hydrogels because they contain lot of water they are responsible for mechanical properties of cells and tissues they regulate passive transport of particles and molecules they serve as lubricants in joints or epithelial surfaces.

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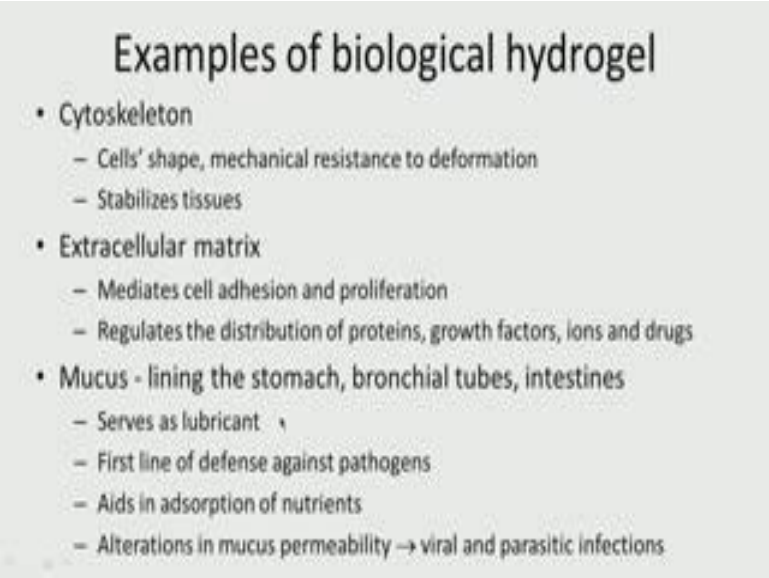

So, what are the examples cytoskeleton; the cell shape mechanical resistance to deformation. So, these prevents mechanical resistance of deformation stabilizes tissues then if you look at the e c m extracellular matrix mediate cell adhesion.

Proliferation regulates the distribution of proteins growth factors ions and drugs these are all extra cellular material mucus lining the stomach bronchial tubes intestine they also take in water and can swell serves as lubricant first line of defense against pathogens aids in absorption of nutrients alteration in mucus permeability viral parasitic infection. So, these are all biological hydrogels mucus extracellular matrix cytoskeleton and so on.

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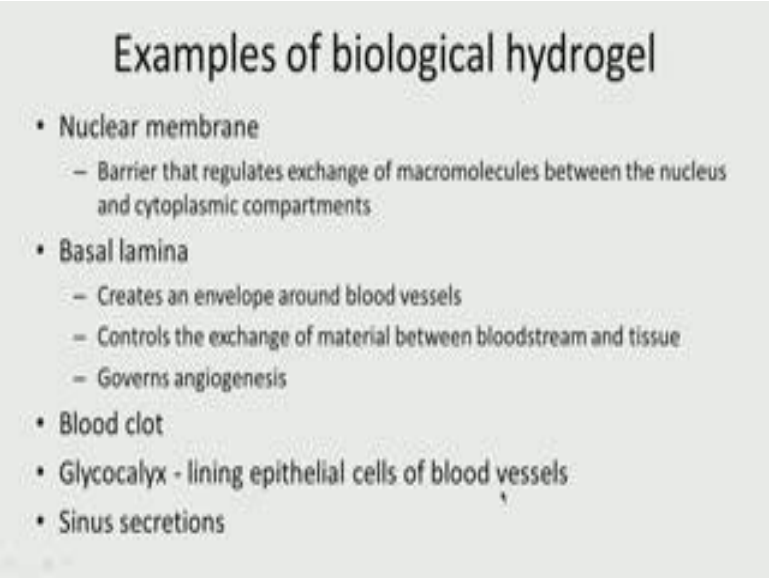

Nuclear membrane barrier that regulates exchange of macromolecules between nuclear and cytoplasmic compartments they are also biological hydrogels basal lamina this creates an envelope around blood vessels controls the exchange of material between blood stream and tissue governs angiogenesis blood clot even that is a hydrogel glycocalyx this is the lining epithelial cells of blood vessels highly hydrophone hydrophilic that is the lining material inside the blood vessels sinus secretion that is also called an hydrogel. So, lot of biological means; that means, inside the body we have plenty of hydrogels and which can swell and lose moisture content and they all serves lot of purpose and they all certain have certain important tasks to perform actually. So, what are the polymers that form hydrogel natural synthetic hyaluronic acid sodium alginate chitosan.

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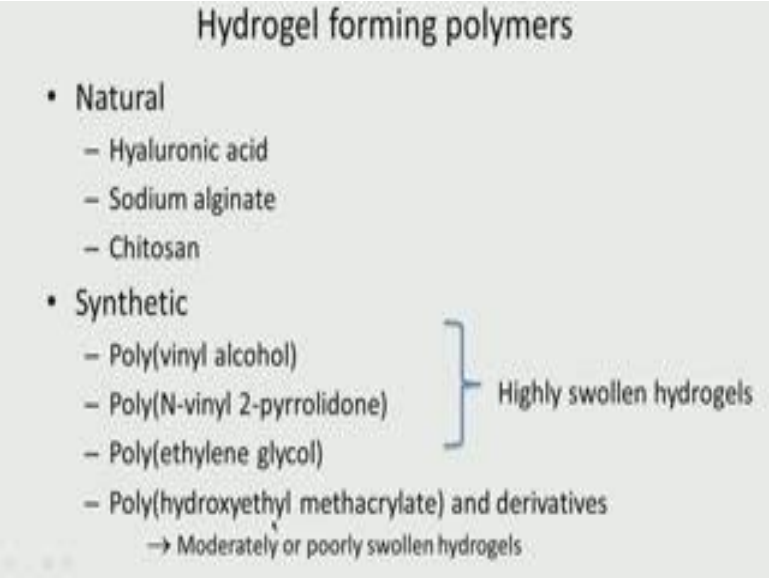

Glucan synthetic PVA poly N-vinyl pyrrolidone: polyethylene glycol poly hydroxyethyl methacrylate and derivatives. So, there lot of these polymers and this polymer moderately or poorly swollen hydrogels they are highly swollen hydrogels this one is poorly swollen. So, lot of polymer. So, we always use these polymers to form hydrogels kerogen forms hydrogel I missed out that glucan that is also a synthetic polymer that also can form jelly type of behavior. So, lot of natural polymers are there synthetic polymers are also there actually. So, sometimes we mix them together to get the correct properties.

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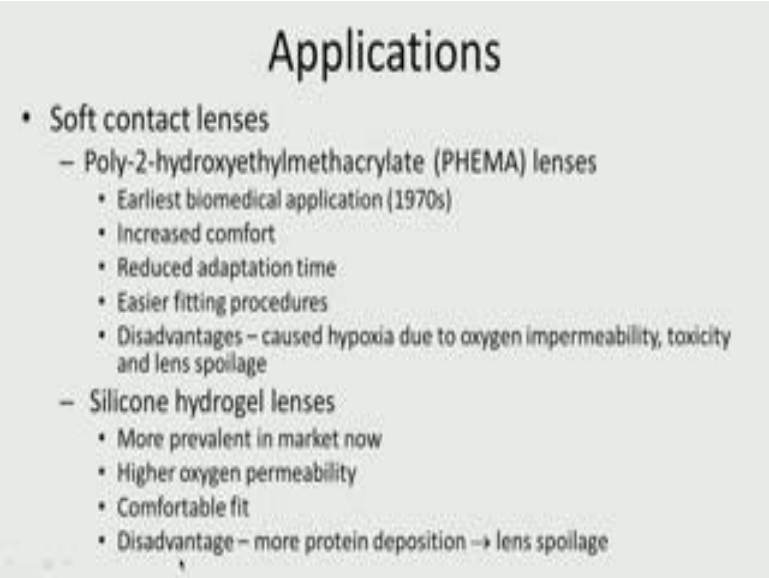

So, applications soft contact lenses poly hydroxyethyl methacrylate these are used in soft contact lenses earliest biomedical application it increases comfort originally they used to use hard contact lenses. So, the eyes get swollen after a couple of hours whereas, the soft contact lenses one can wear it for a very long time reduction reduced adaption time easier fitting procedure disadvantages caused hypoxia due to oxygen impermeability toxicity and lens spoilage silicone hydrogel lenses more prevalent in market now higher oxygen permeability comfortable fit disadvantage more protein disposed deposition the lens spoilage.

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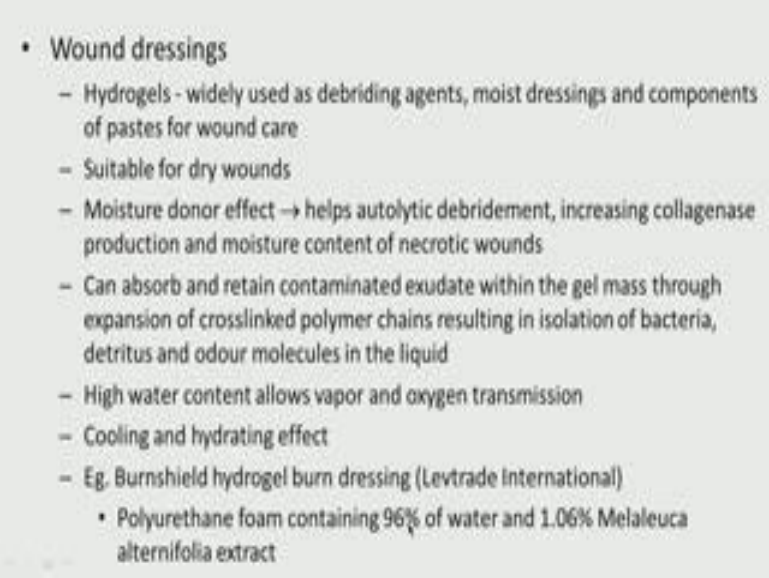

Wound dressing hydrogels are used widely wound dressing moist dressing components of paste for wound care we can have a drug encapsulated wound dressing dry wounds burn wounds and so, we can have moisture donor effect helps autolytic debridement increased collagenous protection and moisture content of necrotic wounds can absorb and retain contaminated exudate within the gel mass through expansion of cross linked polymer chains resulting in isolation of bacteria and odor molecules high water content allows vapor and oxygen transmission.

Cooling and hydrating effect. So, burn shield hydrogel burn dressing polyurethane foam containing 96 percent of water and 1.06 melaleuca alternifolia extract these are used for burn shield wound.

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Product	Main constituents	Characteristics
Granugel (ConvaTec)	Pectin, carboxymethyl cellulose, propylene glycol	Clear, viscous hydrogel for partial and full thickness wounds, provides moist healing environments in dry cavity wounds
Intrasite Gel (Smith & Nephew)	Modified carboxymethyl cellulose, propylene glycol	Amorphous sterile hydrogel for use in shallow and deep open wounds
Purilon Gel (Coloplast)	Sodium carboxymethyl cellulose and more than 90% water	Indicated in conjugation with a secondary dressing for necrotic and sloughy wounds, first and second degree burns
Aquaflo (Covidien)	Polyethylene glycol, polypropylene glycol	Translucent gel that allows visualization, maximizes wound coverage and helps to fill shallow cavities
Woundtab (First Water)	Sulphonated copolymer, carboxymethyl cellulose, glycerol	Superabsorbent polymeric gel for chronic wounds, able to absorb bacteria and retain them in its structure

So, lot of companies make these type of products you can see granugel intrasite gel purilon gel aqua flow wound tab using pectin CMC propylene glycol CMC again propylene glycol sodium CMC polyethylene glycol polypropylene glycol sulphonated. So, they are all used quite a lot in wounds deep wound shallow wounds stick wounds first stage second degree burn wounds quite a lot of wounds all these are products which are in market for all such wounds actually.

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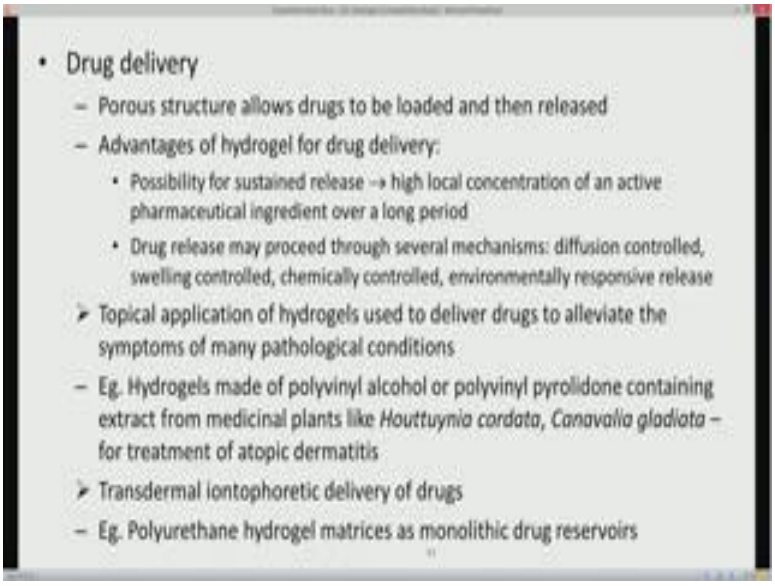

Of course, it can be used for drug delivery also porous structure allows drugs to be loaded and then released possibility for sustained release and we can have different types of mechanism of release diffusion control swelling controlled chemical controlled sorry this is called swelling control chemical control environmental response tropical applications used to deliver drugs to elevate symptoms hydrogels made of PVA polyvinyl pyrolidone containing extracts from medicinal plants for atopic dermatitis. So, lot of drug delivery examples are there.

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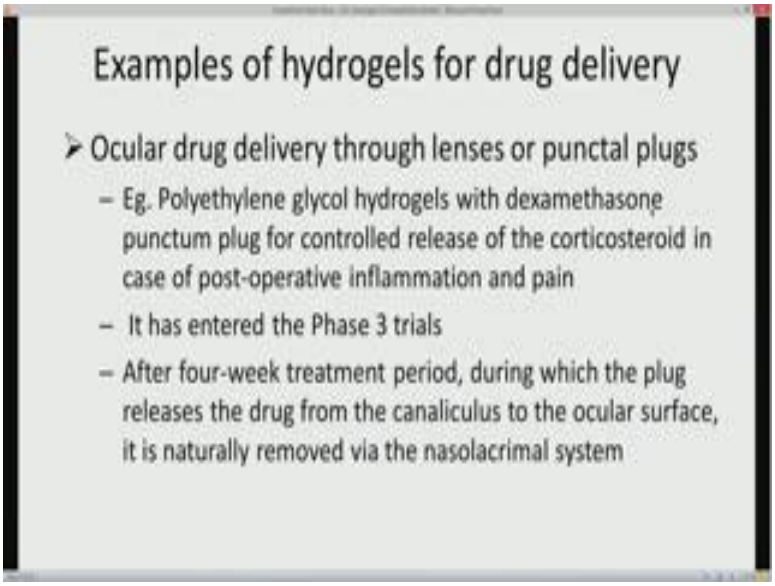

Transdermal delivery of drugs polyurethane hydrogel as monolithic drug reservoirs; so, ocular drug delivery system lenses or punctual plugs polyethylene glycol hydrogels with dexamethasone as an anti-inflammatory as well as pain reliever these are almost switch the phase 3 trials.

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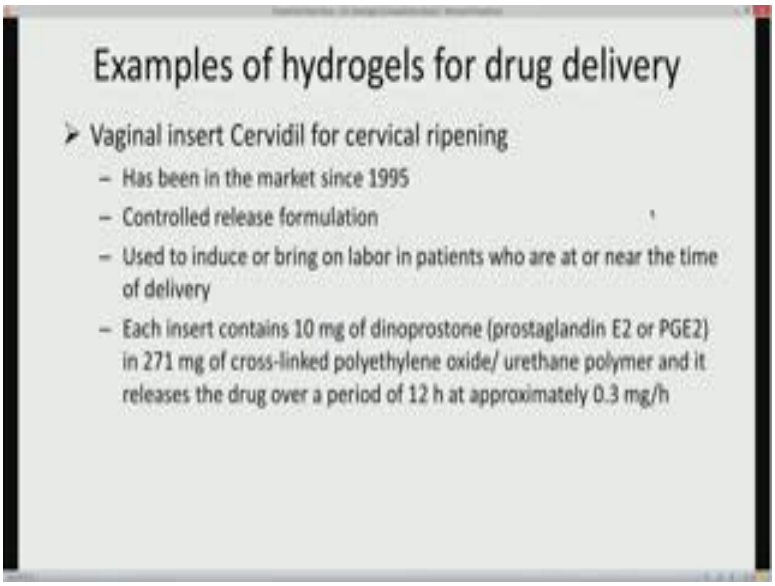

Lot of advantages vaginal insert cervidil for cervical ripening this has been in the market from nineties late nineties controlled release formulation used to induce labor in patients who are at near the time of delivery.

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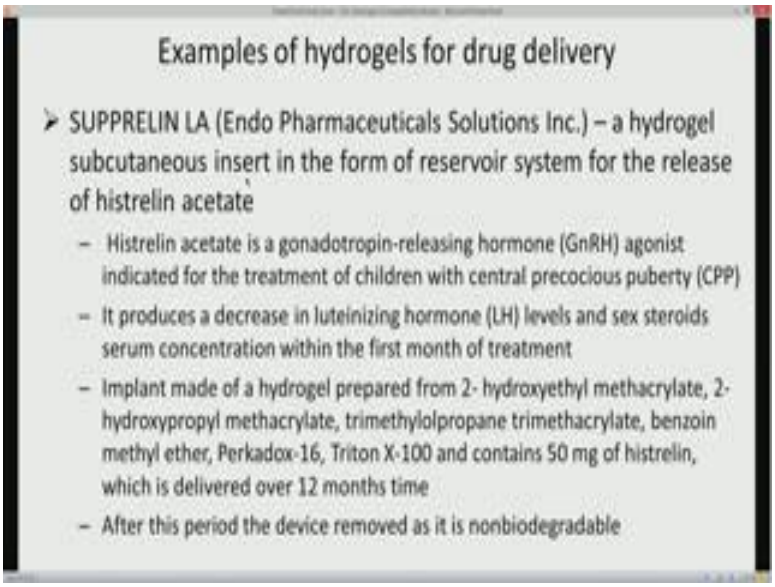

This another example hydrogel for subcutaneous insert in the form of reservoir system for the release of histrelin acetate this is a hormone agonist indicated for the treatment of children with central precocious puberty it produces decrease in a particular hormone l h levels and sex steroids within the first month of treatment. So, this is again a hydrogel

used as a subcutaneous insert. So, there are already many products in the market which makes use of hydrogel tissue engineering.

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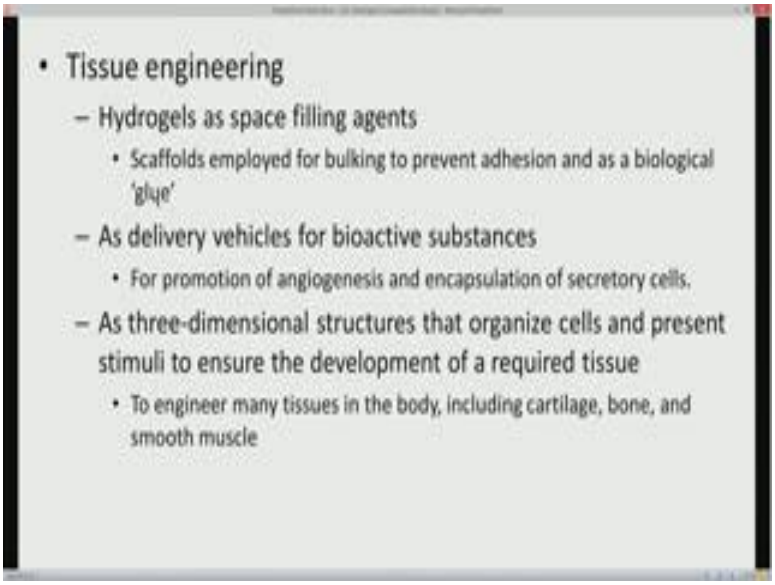

As space filling agent scaffolds to prevent adhesion such as biological clue glue as delivery vehicles for bioactive substances as 3 dimensional structure that organized cells and present stimuli.

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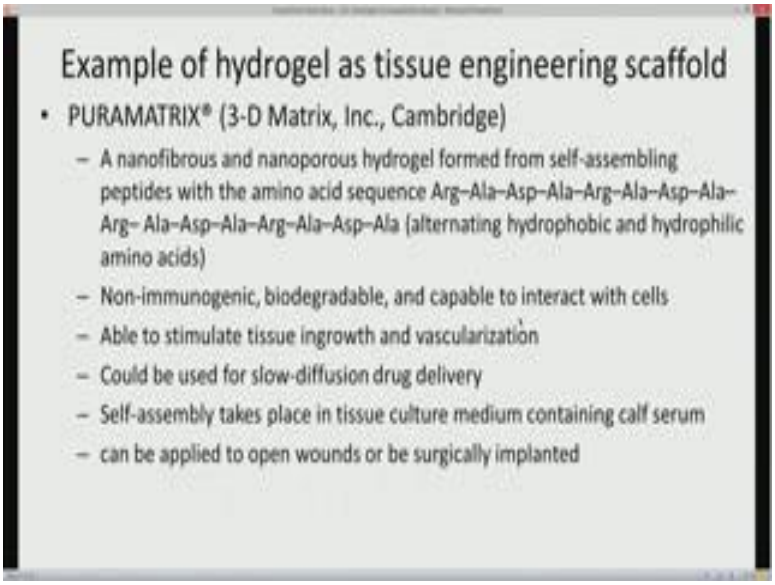

So, a lot of tissue engineering based hydrogels are there and this is the product 3D matrix nanofibrous nanoporous hydrogel formed by self-assembling peptide, arginine, alanine, aspartin.

So, they help in the tissue growth they are not immunogenic biodegradable and capable to interact with cells they are also able to stimulate tissue ingrowth and vascularization could be used for slow diffusion of drugs self assembly properties are also there can be applied for wound.

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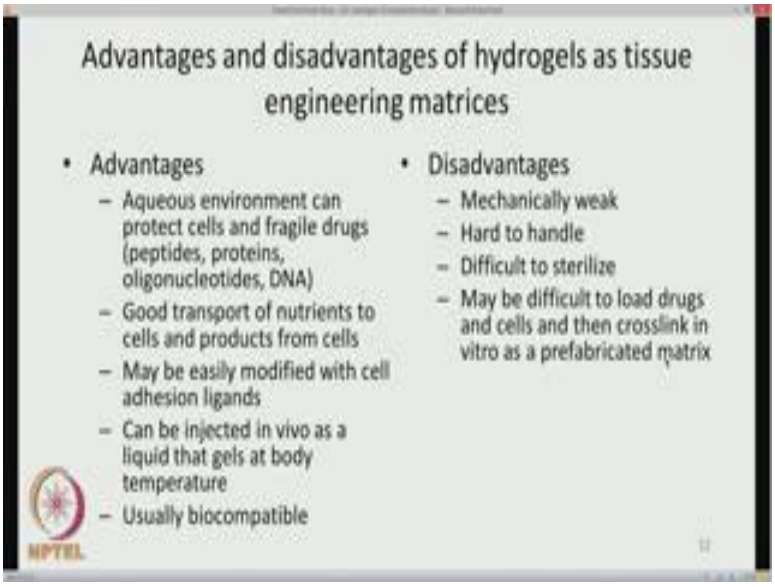

So, tissue engineering advantages we have lot of aqueous environment. So, it can protect cells fragile drugs good transport of nutritions may be easily modified with cell adhesion can be injected also you there you say usually biocompatible main disadvantages they are mechanically very weak hard to handle difficult to sterilize how do we sterilize these type of hydrogels may be difficult to load drugs and cells then cross link in vitro as a prefabricators. So, all these are problems with hydrogels. So, most of the hydrogel applications or topical applications is with subcutaneous application and little bit of drug delivery systems wound based systems and so on actually. So, hydrogels have lot of future especially in this particular area of application.

Thank you very much for your time.