This chapter we will go through what is hydrogel and theory behind hydrogel fabrication. I. Hydrogel introduction.

- II. Hydrogel swell mechanisms
- Hydrogel photo-polymerization III.

Section 1. What is hydrogel?

Hydrogel was first developed in 1950s by Otto Wichterle and Drahoslav Lim [1]. Hydrogel is a tunable 3D networked scaffold of polymers and liquid. Polymers are macromolecular structures, composed of repeated units of monomers that are bonded covalently. When polymers are not crosslinked, they can interact with liquid and form "hydrosol" which is not a solid 3D structure. Crosslinked hydrosols can form solid hydrogels. One distinct characteristic of hydrogel is that it can imbibe large quantities of surrounding liquid and swell to many times (from less than 10, up to 100, and even 1000 times) of the original volume, while maintaining the integrity of its own distinct three-dimensional structure [2,3].

Most hydrogels consist of acrylate and methacrylatesas their backbones [1]. These acrylate families contain at least 2 alkene double bonds (C=C), which are essential for the "polymerization" process covered in section 3. These bonds are also called olefinic double bonds. Hydrogels can be synthesized with naturally occurring materials or manmade chemicals. As hydrogels contain large water contents like natural tissue, they have many important biomedical applications ranging from wound healing [4, 5], drug delivery [6, 7], to cell culturing [8, 9]. As hydrogels can respond to external stimuli, they can be used as sensors [10] responding to changes temperature [11], pH [12], and ions [13]. Hydrogel can also be used as actuators [14] in soft robotics [15, 16] or valve control [17].

Section 2. How does hydrogel swell?

Hydrogels can swell in water drastically without dissolving. The degree of swelling is dominated by osmotic pressure from polymer-solvent interactions, and elastic forces from polymer-polymer interactions. Hydrogel stops swelling when all forces are balanced out. This section gives a brief introduction to all of the forces in a hydrogel system [10].

Osmosis is a spontaneous movement of solvent into a region of higher solute concentration. For the hydrogel system, osmosis can be understood as the process that the solvent water flows into the polymer network to "dissolve" the polymer "solute". Osmotic pressure is thus the minimum pressure to stop such inward water flow. On the other hand, cross-linking is the process to covalently bond polymer chains. These covalent bonds stop hydrogels from expanding infinitely. When these two forces reach an equilibrium, hydrogel remains constant. Lightly crosslinked hydrophilic polymers tend to have larger expansions compared to dense hydrophobic polymer networks.

As mentioned in section 1, Hydrogel can also swell and contract with external stimuli, such as pH, ion concentration, and temperature. Use pH responsive hydrogel as an example where ionic strengths contribute to hydrogel dynamics. When ionizable groups on hydrogel protonate and deprotonate in different pH medium, charge densities within hydrogel networks are modified. When more likewise charges are in a network, nearby branches repulse each other due to coulombic forces, leading to hydrogel expansion. When charge density is decreased, coulombic forces are reduced, leading to hydrogel contraction. The pH sensing range is around the natural pKa of the ionizable polymer but is modified based on the polymer density and co-polymer composition. In addition to the intrinsic polymer material, solvent ion concentration and mobility also affect the ion exchange of the hydrogel and therefore the swelling process. At high solvent ion concentration, osmotic pressure into the hydrogel is reduced, leading to less hydrogel swelling. Therefore, pH sensitive hydrogels usually have application restriction on solvent ion concentration.

To summarize, 4 main forces determine the hydrogel swelling process: osmotic pressure, elastic force, ion coulombic force, and solvent ion osmotic pressure. Hydrogel swelling dynamics are affected by polymer type, network density and solvent types.

There are other important properties for hydrogels depending on the applications. For instance, stiffness for cartilage replacement, fouling for cell handling, and release speed for drug carrier. These are beyond the scope of the document and listed in [18-20]

Section 3. How to make hydrogel?

Photo-induced free radical polymerization and cross-linking are major methods to produce hydrogels and this section gives a quick theoretical overview of this process [1]. Hydrogels are made from pre-polymers including monomer, photo-initiator, and crosslinker. Today, most monomers and crosslinkers can be purchased in liquid form for ease of chemical mixing. Photo-initiators are usually in the powder format. After all chemicals are mixed at a proper ratio, they are ready for light exposure for polymerization and crosslinking.

The main reaction steps for hydrogel formation are initiation, propagation, and termination. During initiation, free radicals are formed from the photo-initiator. The radicals have high energy and can break C=C double bonds on the monomers. The C=C double bond become -C-C- with dangling bonds. These dangling bonds are ready to bond with other dangling bonds. During propagation process, the monomers with broken bonds can bond with each other and thus short monomers are extended into polymers. This bonding between monomers is the polymerization process. Radicals can also attack polymers and polymers can have broken bonds too. The broken bonds on polymer chains can bond with other polymer chains to form a 3D network. This bonding between polymers is the cross-linking process. Once radicals are depleted, the reaction is terminated.

This photo-polymerization process depends on the monomer type, light intensity and time. Acrylate hydrogels react faster than methacrylate hydrogels due to fast diffusion. Photo-initiator can be inhibited by oxygen and thus requires high light intensity to activate. Hydrogels can continue to bond after the light is off, which is the "dark polymerization" process. Therefore, it is important to experiment with each hydrogel and fabrication setup.

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