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EXPLORING STIMULI-SENSITIVE HYDROGELS: INNOVATIONS IN SMART DRUG DELIVERY MECHANISMS

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ABSTRACT
Smart hydrogels are sophisticated materials that react to electric impulses, temperature, pH, and glucose levels, among other external stimuli. The capacity of these hydrogels to release medications at the appropriate time and location has drawn interest in drug delivery systems. Treatments for cancer, eyes, and skin can benefit from temperature-sensitive hydrogels, such as those derived from PNIPAAm, which release medications when they reach body temperature. Hydrogels that are sensitive to pH react to variations in acidity and are perfect for targeted administration in the intestines or stomach.By reacting to blood sugar levels, glucose-sensitive hydrogels assist diabetic patients in managing the release of insulin. When activated externally, other varieties, such electric and light-sensitive hydrogels, provide rapid medication release. Despite their potential, these systems still have issues with immunological responses, limited biodegradability, and delayed response times. Nowadays, research is concentrated on creating hydrogels that are fast-acting, biocompatible, and multiresponsive in order to increase drug delivery accuracy. In the future, these intelligent hydrogels may greatly improve patient care and therapeutic efficacy.

KEYWORDS: Environment-sensitive hydrogels, Drug delivery, Stimuli-sensitive hydrogels.

INTRODUCTION
The drawbacks of traditional drug formulations have been addressed by controlled drug delivery systems which are designed to give medications at specified rates for predefined durations of time even though the field of controlled medication administration has seen tremendous advancements several clinical illnesses including diabetes and rhythmic cardiac problems still require further development in these situations the medicine must be administered in reaction to the bodys changing metabolic needs or the presence of certain biomolecules actually the best outcome would be for the medications to be administered in a way that exactly satisfies physiological demands at the right times temporal modulation andor at the right location site-specific targeting. Additionally, methods for delivering peptide and protein medications need to be further developed in the controlled drug delivery field. The body uses a feedback system known as "homeostasis" to regulate the appearance of many bioactive peptides in order to preserve a proper metabolic balance. If the active ingredients were administered by a system that detected the signal resulting from illness, assessed its strength, and then responded by releasing the appropriate dosage of medication, that would be extremely advantageous. A feedback mechanism would be needed to link the drug delivery rate with the physiological need in such a system. The creation of intelligent medication delivery systems has made substantial use of hydrogels. A network of hydrophilic polymers that can retain their structure while swelling in water is called a hydrogel. When polymer chains are crosslinked, a three-dimensional network is created. Van der Waals interactions, hydrogen bonds, covalent connections, and physical entanglements can all produce crosslinking. Hydrogels can shield the medication from harsh conditions, such as the stomach's low pH and the presence of enzymes. By altering the gel structure in response to external stimuli, hydrogels can also regulate the release of drugs. Hydrogels When the environment changes even slightly, hydrogels with these "sensor" qualities can experience reversible volume phase transitions or gel–sol phase transitions. "Intelligent" or "smart" hydrogels are other names for the kinds of environment-sensitive hydrogels. Numerous chemical and physical stimuli have been used to cause the smart hydrogel systems to react in different ways. While pH, ions, and particular molecular recognition events are examples of chemical or biochemical stimuli, temperature, electric fields, solvent composition, light,

pressure, sound, and magnetic fields are examples of physical stimuli. Applications for smart hydrogels are numerous and include the creation of chemical valves, artificial muscles, enzyme and cell immobilization, and the concentration of diluted solutions in bioseparation. Hydrogels that are sensitive to the environment are excellent building blocks for self-regulating medication delivery systems. In this chapter, environmentally sensitive hydrogels are categorized for convenience according to the kind of stimuli.

Hydrogels That Are Sensitive To Temperature

1) Polymer Structures

In drug delivery research, temperature-sensitive hydrogels are arguably the most extensively researched family of environmentally sensitive polymer systems. A temperature-responsive phase transition feature is present in many polymers. Fig. 1 displays the structures of a few of those polymers. Hydrophobic groups, including methyl, ethyl, and propyl groups, are a typical feature of temperature-sensitive polymers. The most widely utilized of the several temperature-sensitive polymers is most likely poly(N-isopropylacrylamide) (pnipaam). Because of its lower critical solution temperature (LCST), which is in the range of 25 to 32 °C, or near body temperature, poly(N, N-diethylacrylamide) (pdeaam) is also commonly employed. To change the LCST, copolymers of nipaam can also be created with other monomers, such as butyl methacrylate (BMA). Inverse temperature sensitivity is another characteristic of several poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) block copolymer varieties. They have been extensively utilized in the creation of controlled drug delivery systems based on the sol–gel phase conversion at body temperature due to their LCST at about body temperature. Pluronics ® (also known as Poloxamers ®) and Tetronics ® are the names of several PEO–PPO block copolymers that are sold commercially. In Fig. 2, their structures are displayed.

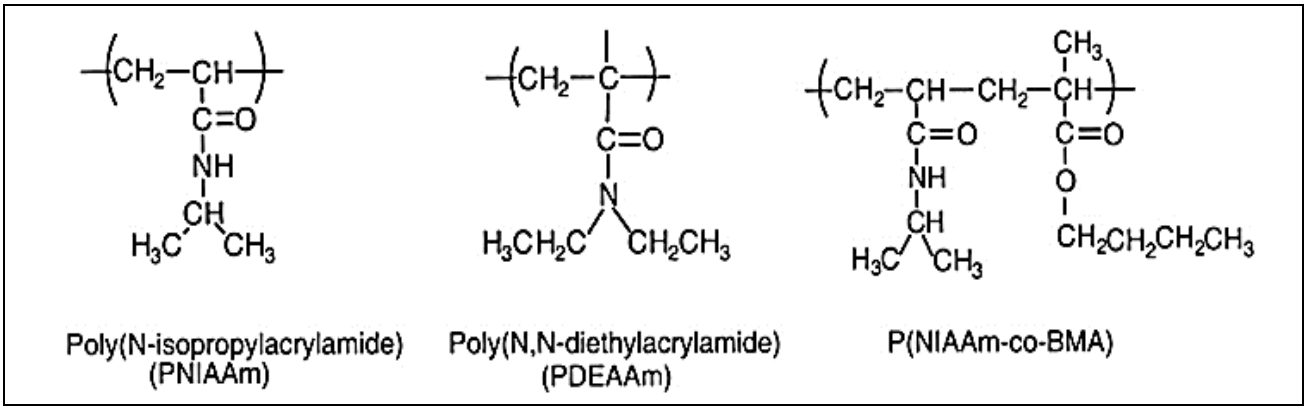

Fig. 1: Structures of some polymers that are sensitive to temperature.

Source:https://www.researchgate.net/publication/307437266/figure/fig10/AS:611264476741639@1522748216620/Structures-of-some-temperature-sensitive-polymers.png

2) Features Of Hydrogels That Are Responsive To Temperature

Most polymers improve their water-solubility as the temperature increases. However, when the temperature rises, polymers having LCST become less soluble in water. As the temperature rises above the LCST, LCST polymer-based hydrogels contract. Inverse (or negative) temperature dependency is the term used to describe this kind of swelling behavior. The polymer chains that make up the inverse temperature-dependent hydrogels either have a mixture of hydrophilic and hydrophobic segments or have moderately hydrophobic groups (if excessively hydrophobic, the polymer chains would not dissolve in water at all). Hydrogen bonds between water molecules and hydrophilic portions of the polymer chain predominate at lower temperatures, which improves dissolution in water. However, hydrophobic interactions between hydrophobic segments get stronger and hydrogen bonding gets weaker as the temperature rises. As a result of inter-polymer chain connection through hydrophobic interactions, the hydrogels ultimately shrink. Generally speaking, LCST decreases when the polymer chain contains more hydrophobic constituents. The ratio of the polymer's hydrophilic to hydrophobic segments can be altered to alter the LCST. Making copolymers of hydrophilic (like acrylic acid) and hydrophobic (like NIPAAm) monomers is one method. It is known that adding a tiny quantity of ionizable groups to the gel network or altering the solvent composition can cause the continuous phase transition of PNIPAAm to become discontinuous. When NIPAAm is copolymerized with other monomers, hydrogels with more adaptable characteristics are produced, including sensitivity to other stimuli and quicker rates of shrinkage when heated through the LCST.

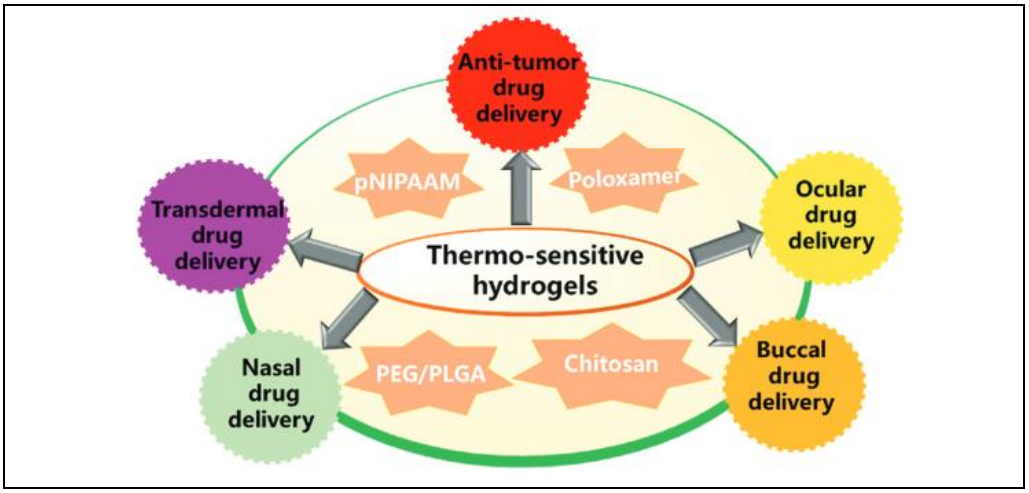

Fig. 1(A): Schematic illustration of the structure of this review.

Source:https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcRQao3prApoDqrGJvlFo4FeRs0YGpzbeNu4tw&s

Temperature-sensitive hydrogels may experience sol–gel phase transitions rather than swelling–shrinking transitions if the polymer chains are not covalently crosslinked. At higher temperatures, the thermally reversible gels with an inverse temperature dependency dissolve. Block copolymers of PEO and PPO are polymers that exhibit this kind of activity, as seen in Fig.

2. Other hydrophobic polymers can be used in lieu of the hydrophobic PPO block. For instance, poly(lactic acid) block copolymers containing PEO have the same thermo-reversible characteristic. The poly(lactic acid) section in this instance offers a biodegradable characteristic.

POLYMER [A]	***LCST*** (^{0}***C***)
PNIPAAM	**32**
PEG	**120**
PPG	**50**
MC	**80**

Fig 1(B):- The LCSTs of typical negative thermo-sensitive polymers.

Source:https://scholar.google.co.in/scholar?q=The+LCSTs+of+typical+negative+thermo-sensitive+ polymers & hl=en&as_sdt=0&as_vis=1&oi=scholart

Temperature-sensitive crosslinking agents can also be used to create temperature-sensitive hydrogels. A well-defined protein-folding motif, the coiled coil, and water-soluble synthetic polymers were combined to create a hybrid hydrogel system. The coordinated conformational change caused the hydrogel to collapse as a result of temperature. Designing temperature-sensitive hydrogels takes on a new dimension with the use of temperature-sensitive crosslinking agents.

❖ ***TEMPERATURE-SENSITIVE HYDROGEL APPLICATIONS***

1) The mechanism of injectable depot systems: given as a liquid at room temperature, it turns into a gel at body temperature.

Benefit: Creates a drug depot at the intended location with little invasiveness.

Use: Long-term hormone, antibiotic, and anti-inflammatory medication release.

Example: Insulin-loaded injectable hydrogel for long-term glucose regulation.

2) Thermo-triggered drug release in cancer therapy

Mechanism: Small local temperature changes (such as in malignancies) cause drug release.

Benefit: Reduces systemic toxicity and improves localized delivery.

Application: Chemotherapeutic drugs administered to solid tumors, such as doxorubicin. For instance, hydrogels based on thermo-responsive PNIPAAm for tailored release of cancer drugs.

3) Ocular Drug Delivery Mechanism: When eye drops come into touch with the eye, they solidify into a gel.

Benefits include increased medication bioavailability and longer residence duration.

Use: glaucoma medicines, antibiotics, and anti-inflammatory treatments. For instance, in-situ gelling formulations that administer timolol continuously.

4) Transdermal Drug Delivery Mechanism: Topically placed, temperature-sensitive gels that release medications when body heat triggers gelation.
Benefits include less inflammation and improved penetration.
Uses include hormone treatments and pain reliever gels.

5) Drug delivery mechanism for the vagina and rectal area: liquid at room temperature, gels after administration because of body heat.
Benefits include better patient comfort and targeted, sustained delivery.
Use: The administration of antiviral, antibiotic, or contraceptive medications.

❖ ***NEGATIVELY THERMO SENSITIVE DRUG RELEASE SYSTEMS***

To get an on-off drug release profile in response to a gradual temperature change, thermo sensitive monolithic hydrogels were employed. Cross-linked p(nipaam–co-bma) hydrogels and interpenetrating polymer networks (ipns) of p(nipaam) and poly(tetra methylene ether glycol) (ptmeg) are among the hydrogels utilized in these investigations. To improve the mechanical strength of nipaam gels, the hydrophobic commoner bam was added. These matrices produced an on-off release profile of indomethacin, which was on at low temperatures and off at high ones. The development of a thick, less permeable gel surface layer—dubbed a skin-type barrier—was cited as the explanation. Because the gel surface collapsed more quickly than the inside, the skin barrier was created following an abrupt temperature shift. It was discovered that the length of the methacrylate alkyl side-chain, or the commoner's hydrophobicity, controlled this surface shrinking process. Even in cases where no drug release was seen, the data still suggested that the drug in the polymeric matrix diffused from the inside to the surface during the off state.

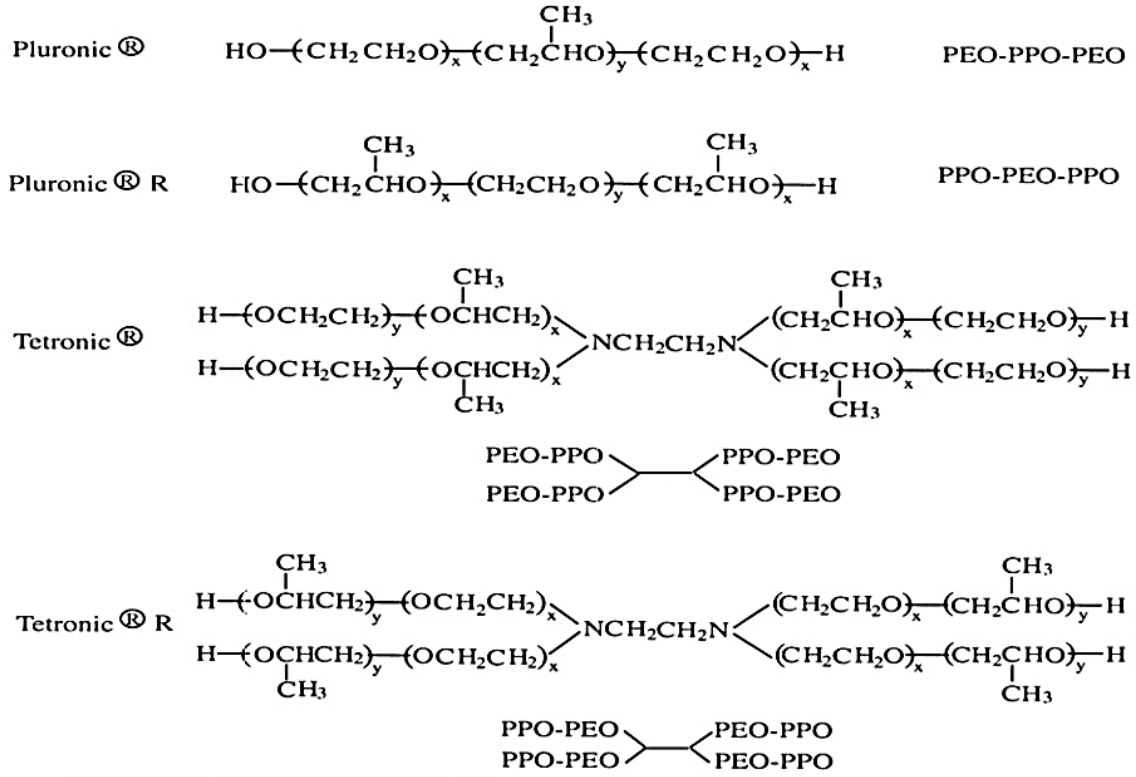

Fig. 2: Polymer structures of Pluronic ®, Pluronic ® R, Tetronic ® and Tetronic ® R.

Source:https://www.sciencedirect.com/topics/chemistry/pluronic#:~:text=Pluronics%20are%20amphiphilic%20nonionic%20triblock,units%20in%20the%20block%20copolymer.

It is also possible to enclose temperature-sensitive hydrogels in a stiff capsule with openings or holes. Temperature-sensitive hydrogels' reversible volume change allows for the on-off release, as seen in Fig. 3. Because the hydrogel dimension affects the drug release, this type of device is known as a squeezing hydrogel device. Hydrogels may be engineered to react not just to temperature but also to other stimuli like pH. The rate at which the drug-loaded polymer squeezed was found to be related to the drug release rate in this kind of system. Grafting temperature-sensitive hydrogels to the surface of stiff membranes or encasing them within a hard matrix are two methods of securing them. PNIPAAm was dispersed to create a composite membrane.

Hydrogel microparticles into a gelatin matrix that has been crosslinked. The temperature that dictated the swelling state of the PNIPAAm hydrogel microparticles in the membrane's microchannels influenced the release of a model drug, 4-acetamidophen. A reservoir-type microcapsule drug delivery system was created using a similar methodology, which involved encasing the drug core in ethylcellulose that contained nano-sized PNIPAAm hydrogel particles. PNIPAAm hydrogel may be grafted across the whole surface of a rigid porous polymer membrane to create reliable thermally regulated on-off devices.

❖ *POSITIVELY THERMOSENSITIVE DRUG RELEASE SYSTEMS*

IPN-formed hydrogels exhibit positive thermosensitivity, meaning they swell at high temperatures and contract at low ones. The swelling of IPNs of poly(acrylic acid) and polyacrylamide (PAAm) or P(AAmco-BMA) changes positively with temperature. A greater transition temperature was achieved by increasing the BMA concentration. Those hydrogels responded to gradual temperature changes by swelling in a reversible manner. As a consequence, a monolithic device's release rate of the model medication ketoprofen changed reversibly.

❖ *GELS THAT ARE THERMOREVERSIBLE*

Tetronics ® and Pluronics ® are the two thermoreversible gels that are most frequently utilized. The FDA and EPA has authorized a few of them for use in medicinal compounds, food additives, and agricultural items. There is a summary of Pluronics ®'s characteristics and uses in medication administration. It is ideal for thermoreversible gels to be biodegradable for parenteral administration. The PPO segment of PEO–PPO–PEO block copolymers is frequently swapped out for a biodegradable poly(L-lactic acid) segment to increase biodegradable capacity. The molecular architecture developed into three-dimensional, hyperbranched structures, like a star-shaped structure, rather than being restricted to the A–B–A type block copolymer. The right combinations of polymer architecture and molecular weight produced gels with varying LCST values. The release of a hydrophilic model drug (ketoprofen) and a hydrophobic model drug (spironolactone) were first-order and S-shaped, respectively, when the hydrogel was created by injecting the polymer solution containing the model medicines into an aqueous environment at 37 °C.

❖ *RESTRICTIONS AND ENHANCEMENTS*

There are restrictions on the clinical use of thermosensitive hydrogels based on NIPAAm and its derivatives. It is unknown if the monomers and crosslinkers employed to create the hydrogels are biocompatible; instead, they may be teratogenic, poisonous, or carcinogenic. Furthermore, NIPAAm and its derivatives' polymers are not biodegradable. Prior to the emergence of therapeutic applications, comprehensive toxicity investigations are necessary due to the finding that acrylamide-based polymers activate platelets upon contact with blood and the uncertain metabolism of poly(NIPAAm). To fully use the beneficial qualities of thermoreversible hydrogels, greater research and development of novel, biocompatible, and biodegradable thermoreversible gels—like PEO–PLA block copolymers—is required.

❖ *PH-SENSITIVE HYDROGELS*

❖ *POLYMER STRUCTURES*

Pendant acidic (such as carboxylic and sulfonic acids) or basic (such as ammonium salts) groups are present in all PH-sensitive polymers, and they react to variations in the surrounding PH by either accepting or releasing protons. Polyelectrolytes are polymers that include a lot of ionizable groups. Examples of cationic and anionic polyelectrolyte structures and their ph-dependent ionization are displayed in Fig. 4. At high PH, poly(acrylic acid) (PAA) ionizes, but at low ph, poly(N,N′-diethylaminoethyl methacrylate) (PDEAEM) ionizes. As seen in Figure 4, ionization causes cationic polyelectrolytes, such PDEAEM, to dissolve more readily or swell more when crosslinked at low PH. However, polyanions like PAA dissolve more readily at high PH values.

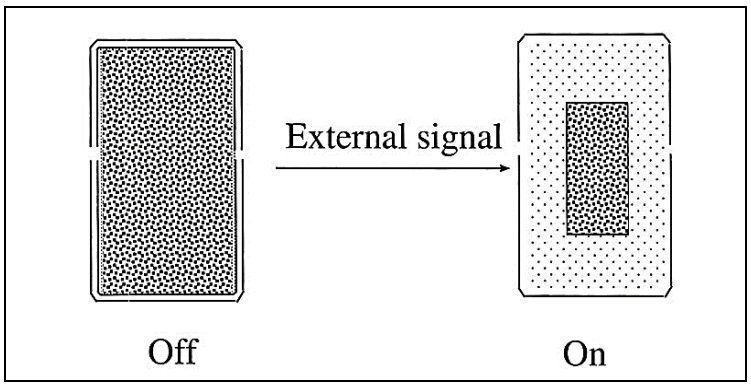

Fig. 3: Schematic illustration of on–off release from a squeezing hydrogel device for drug delivery.

Source:https://slideplayer.com/slide/13884618/85/images/4/Schematic+illustration+of+on%E2%80%93off+release+from+a+squeezing+hydrogel+device+for+drug+delivery.jpg

❖ ***CHARACTERISTICS OF HYDROGELS THAT ARE PH-SENSITIVE***

The swelling characteristics of hydrogels composed of crosslinked polyelectrolytes vary significantly based on the ambient pH. Similar to the acidic or basic groups of monoacids or monobases, the pendant acidic or basic groups on polyelectrolytes are ionized. However, the electrostatic effects of other nearby ionized groups make ionization on polyelectrolytes more challenging. The apparent dissociation constant (Ka) tends to differ from that of the corresponding monoacid or monobase as a result. When ionizable groups are present on polymer chains, the hydrogels expand far more than nonelectrolyte polymer hydrogels can. Given that the electrostatic repulsion between charges on the polymer chain is the primary cause of swelling in polyelectrolyte hydrogels, any circumstance that decrease electrostatic repulsion, including counterion type, ionic strength, and pH. Maleic anhydride, methyl methacrylate, 2-hydroxyethyl methacrylate, and other neutral comonomers can be used to modify the swelling and pH responsiveness of polyelectro-lyte hydrogels. Various comonomers provide the polymer chain varying degrees of hydrophobicity, which results in varying pH-sensitive behaviors.

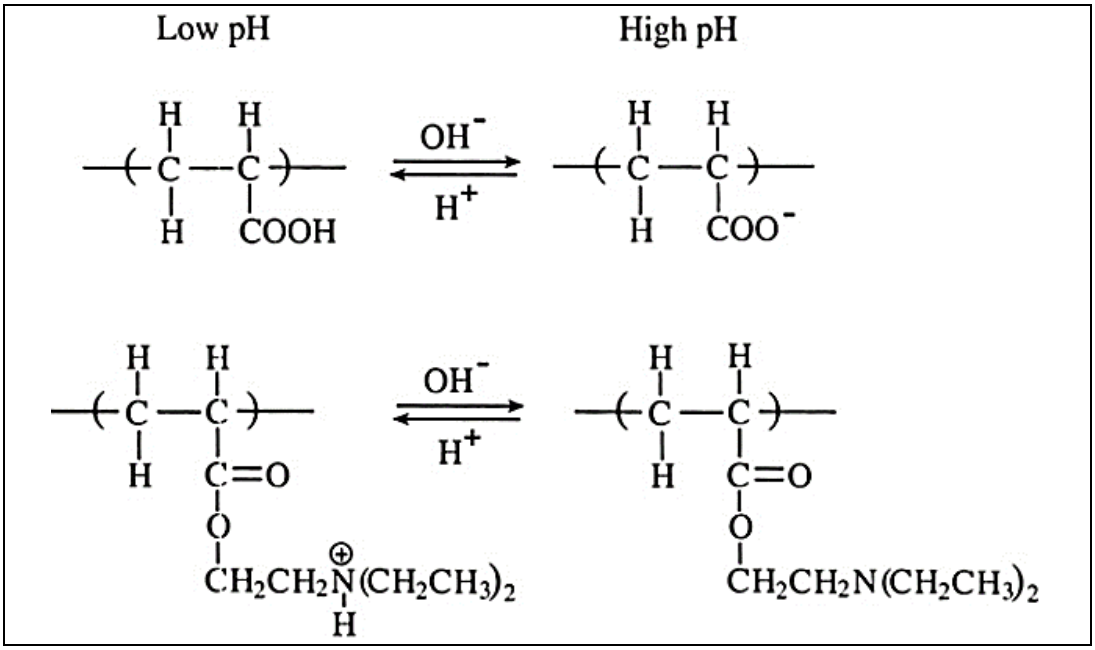

Fig. 4: pH-dependent ionization of polyelectrolytes. Poly (acrylic acid) (top) and poly (N, N′-diethylaminoethyl methacrylate) (bottom).

Source:

Hydrogels composed of poly(ethylene glycol) (PEG) grafted onto poly(methacrylic acid) (PMA) exhibit special ph-sensitive characteristics. When the ph is low, the hydrogels shrink as a result of the complexation between the ether oxygen of PEG and the acidic protons of PMA's carboxyl groups. The hydrogels expand as a result of the decomplexation that occurs when the carboxyl groups of PMA are ionized at high ph. IPN systems, in which two distinct kinds of polymer chains connect via ph-dependent hydrogen bonding, can benefit from the same idea.

APPLICATIONS OF PH-SENSITIVE HYDROGELS

❖ ***CONTROLLED DRUG DELIVERY***

The most common application of pH-sensitive hydrogels has been in the creation of oral controlled release formulations. The stomach's pH (b3) differs significantly from the intestine's neutral pH, and this difference is significant enough to cause polyelectrolyte hydrogels to exhibit pH-dependent behavior. Drug release from polyatomic hydrogels is minimized because of their limited swelling at neutral pH. This characteristic has been employed to stop bad-tasting medications from leaking into the mouth's pH-neutral environment. Caffeine was released at zero-order at pH 3–5, when DMAEM became ionized, rather than at neutral pH when it was put into hydrogels composed of copolymers of methyl methacrylate and N, N′-dimethylaminoethylmethacrylate (DMAEM). Drug distribution in the stomach has also made use of semi-IPN polycationic hydrogels. PEO and cross-linked chitosan semi-IPN exhibited increased edema in acidic environments (such as the stomach). For the localized administration of medicines, such as amoxicillin and metronidazole, in the stomach to treat Helicobacter pylori, these hydrogels would be perfect.

Formulations that release medications in a pH-neutral environment can be created using hydrogels composed of PAA or PMA. For colon-specific medication administration, hydrogels composed of polyanions (such as PAA) crosslinked with azoaromatic crosslinkers were created. Such hydrogels cause very little stomach swelling, which results in very little drug release. As the hydrogel travels through the intestinal tract, the amount of swelling increases because the pH rises and the carboxylic groups get ionized. However, as Fig. 5 illustrates, azoreductase generated by the colon's microbial flora can only break down the azoaromatic cross-links of the hydrogels in the colon. The crosslinking density can regulate the rate of deterioration and the pattern of degradation (such as bulk or surface erosion). The composition of the polymer may be altered to regulate the kinetics of hydrogel swelling. Changes in the environment's pH can alter the composition of the polymer. As the pH shifts from acidic to neutral, some pendant groups, including N-alkanoyl (such as propionyl, hexanoyl, and lauroyl) and O-acylhydroxylamine moieties, can hydrolyze. The length of the alkyl moiety affects the rate of side-chain hydrolysis.

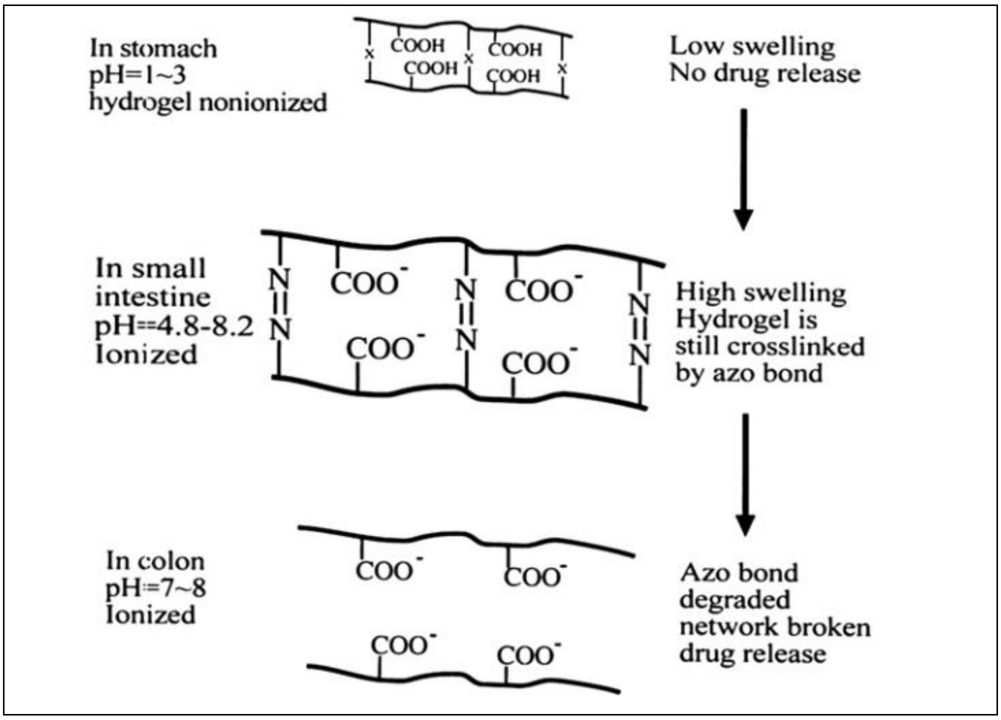

Fig. 5: Schematic illustration of oral colon-specific drug delivery using biodegradable and pH-sensitive hydrogels. The azoaromatic moieties in the cross-links are designated by –N_N–

Source:

To control the drug release, pH-sensitive hydrogels were inserted inside silicone matrices or capsules. Drug release in the compressing hydrogel system was regulated by a manner like that depicted in Figure 3. The sole distinction is that pH, rather than temperature, regulates the swelling and contracting of hydrogels. Semi-IPN hydrogel particles of PAA and PEO were employed in the silicone matrix system to mediate pH. The semi-IPN's pH-dependent swelling pattern was linked to the release patterns of a number of model medications with varying aqueous solubilities and partitioning characteristics, such as salicylamide, nicotinamide, clonidine HCl, and prednisolone. The release was restricted to an early burst and the network swelling was minimal at pH 1.2. The network became ionized at pH 6.8, and more swelling led to greater release. PVD, or poly(vinylacetaldiethylaminoacetate), is soluble in water at varying pH values. When the pH was raised from 4 to 7.4, PVD developed a hydrogel, according to the turbidity and SEM data. When the PVD solution was added to a pH 7.4 buffer solution, the release of a model drug, chlorpheniramine maleate, was rapid at first, but it slowed significantly once the PVD hydrogel was created. Nasal spray dosage formulations were created using the pH-dependent sol-to-gel transformation of AEA to treat sinusitis and allergic rhinitis. According to the in vivo rat investigation, when the concentration of PVD increased, the apparent disappearance rate constant of chlorpheniramine maleate decreased. It was clearly verified that hydrogel had formed on the mucous membranes of the rat's nasal cavity. The PVD method could be the best option for

nasal administration if the sol-to-gel transition period is decreased and the mucoadhesive feature is included.

❖ *OTHER APPLICATIONS*

Permeation switches and biosensors have also been made with pH-sensitive hydrogels. Enzymes that alter the pH of the local microenvironment inside the hydrogels are typically added to pH-dependent hydrogels for these uses. Glucose oxidase, an enzyme that converts glucose to gluconic acid, is frequently utilized in pH-sensitive hydrogels. The swelling of pH-dependent hydrogels is impacted by the local pH being lowered by the production of gluconic acid.

❖ *LIMITATIONS AND IMPROVEMENTS*

The non-biodegradability of artificial pH-sensitive polymers is one of their fundamental drawbacks. Hydrogels composed of non-biodegradable polymers must thus be eliminated from the body after usage. In certain applications, like oral medication administration, the non-biodegradability is not an issue; but, in other applications, such the creation of implanted drug delivery agents or implantable biosensors, it becomes a significant barrier. The creation of pH-sensitive, biodegradable hydrogels based on proteins, polypeptides, and polysaccharides has therefore received attention.4-aminobutyric acid was used to activate dextran in order to crosslink it with 1,10-diaminodecane and graft it with carboxylic groups. At high pH levels, the modified dextran hydrogels swelled more quickly and to a greater extent; cyclic swelling–deswelling occurred when the pH was changed from 7.4 to 2.0. It should be mentioned that because the body or certain locations within the body could not have the enzyme necessary to break down dextran molecules, dextran hydrogels might not be completely biodegradable. The human body may not always be able to biodegrade natural polysaccharides.

❖ *GLUCOSE-SENSITIVE HYDROGELS*

The creation of self-regulated (modulated) insulin administration systems is one of the most difficult issues in the field of controlled medication delivery. The way insulin is provided differs from that of other medications since it must be administered precisely when needed. Therefore, glucose detecting capability and an automated shut-off mechanism are necessary for self-regulated insulin administration systems. A glucose sensor is included into each of the several hydrogel systems that have been created to control the administration of insulin.

❖ *PH-SENSITIVE MEMBRANE SYSTEMS*

The enzyme most frequently used in glucose sensing is most likely glucose oxidase. It changes the environments pH by oxidizing glucose to gluconic acid. This enables the use of several pH-sensitive hydrogel types for insulin delivery that is regulated. The ionization of PDEAEM causes the hydrogel membrane to expand when the pH is lowered for hydrogel membranes composed of polycations like PDEAEM. A membrane that swells has a tendency to release more medications, such as insulin, than one that is less swollen. outcome of the pH being lowered. In this instance, the collapsing hydrogel's "squeezing" effect increases insulin release. When a pH-sensitive erodible polymer holding insulin is covered by a hydrogel containing glucose oxidase, the local pH must be lowered to limit polymer erosion and, therefore, insulin release.

❖ *CON A-IMMOBILIZED SYSTEM*

Modulated insulin administration has also made extensive use of Concanavalin A (Con A). Con A is a glucose-binding protein that is derived from Canavalia ensiformis, a plant that produces jack beans. Insulin molecules are joined to a support or carrier in this kind of system by certain connections that glucose itself can break. Usually, this calls for adding functional groups to insulin molecules. One method included chemically altering insulin to add glucose, which specifically binds to Con A.Con A's complimentary and competitive binding activity with glucose and glycosylated insulin is exploited by the glycosylated insulin–Con A system. In the presence of free glucose, the glycosylated insulin is desorbed from the Con A host due to competition between the free glucose molecules and glucose–insulin conjugates attached to Con A. Studies have indicated that the desorbed glucose–insulin conjugates are bioactive when they are released into the surrounding tissue. To control the displacement of immobilized insulin from Con A at varying glucose levels, many glycosylated insulins with varying binding affinities to Con A have been created.

❖ *SOL–GEL PHASE REVERSIBLE HYDROGEL SYSTEMS*

Depending on the amount of glucose present, hydrogels may be engineered to go through sol–gel phase changes. Crosslinking that is sensitive to glucose is necessary for reversible sol–gel phase transitions. Crosslinks between glucose-containing polymer chains were created by a very particular interaction between glucose and Con A. Con A can act as a crosslinking agent for glucose-containing polymer chains since it is a tetramer at physiological pH and each subunit possesses a glucose binding site. The resulting crosslinks are reversible due to the non-covalent interaction between glucose and Con A, as seen in Fig. 6.Individual free glucose molecules may compete and exchange with the polymer-attached glucose molecules as the external glucose molecules permeate the hydrogel. Hydrogels that react (i.e., go through gel-to-sol transformation) at particular free glucose concentrations may be created by varying the concentrations of Con A and glucose-containing polymers. It has been demonstrated that insulin can be modulated in response to environmental glucose concentrations and that its diffusion through the solution (Sol) phase is an order of magnitude quicker than that via the hydrogel (gel) phase. Poly (glucosyloxyethylmethacrylate)–Con A complexes and polysaccharides (such as polysucrose, dextran, and glycogen)–Con A gel membranes were used in other

comparable systems. agent for crosslinking. Several copolymers containing phenylboronic acid were created to give glucose sensitivity at physiological pH since the phenylboronic acid gel is only sensitive to glucose under alkaline circumstances (pH 9). The low specificity of PBA-containing polymers to glucose is the system's primary issue. As a result, the gel's crosslinking density falls and it swells or erodes to release more insulin as the glucose concentration rises. The gel turns into a sol with greater glucose concentrations. At lower glucose concentrations, borate-polyol crosslinking is repaired and the glucose exchange process is reversible. Diglucosylhexanediamine and other shorter molecules can be used in place of long chain polyol polymers.

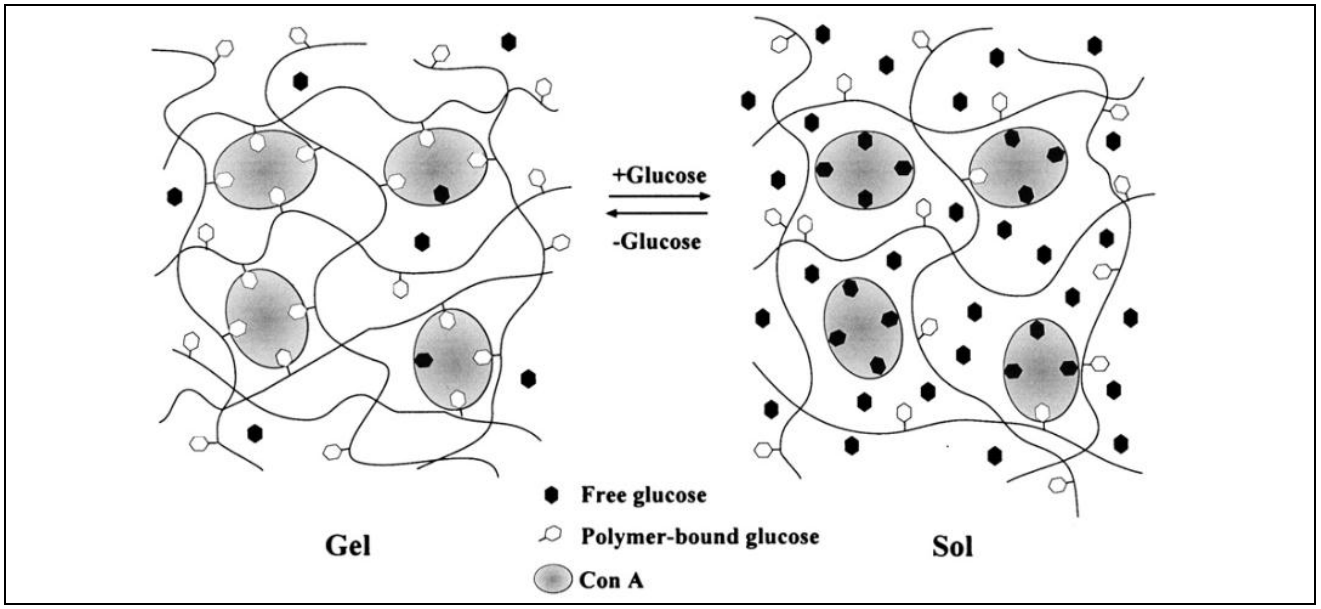

Fig. 6:- Sol–gel phase-transition of a glucose-sensitive hydrogel. Large circles represent Con A, a glucose-inding protein. Small open and closed hexagons represent polymer-attached glucose and free glucose, respectively.

Source:http://kinampark.com/KPTopics/files/Hydrogels,%20Glucose-sensitive/1996%20Lee%20Synthesis%20and%20characterization%20of%20sol-gel%20phase-reversible%20hydrogels%20sensitive%20to%20glucose.pdf

❖ ***LIMITATIONS AND IMPROVEMENTS***

All of the glucose-sensitive insulin delivery devices are stylish and extremely promising, but they still require a lot of work before they can be used in clinical settings. In the first place, these hydrogels react too slowly to variations in the ambient glucose content. Furthermore, hydrogels do not revert back to their original states fast enough after reacting to the changing glucose concentration. One strategy to speed up the reaction time might be to reduce the hydrogel's size. Additionally, the reproducibility of the existing hydrogel systems has to be addressed. In clinical settings, hydrogels must react constantly to fluctuating glucose concentrations, necessitating the use of hydrogels with long-term, repeatable responses and quick reaction start times. Con A, the crosslinker most commonly employed in modulated insulin administration, is known to trigger an unwanted immunological response, which is another restriction. All of the components utilized in the glucose-sensitive hydrogels must be biocompatible. The development of novel, biocompatible glucose-binding compounds is necessary for the successful clinical use of glucose-sensitive hydrogels for regulated insulin administration.

➢ ***ELECTRIC SIGNAL-SENSITIVE HYDROGELS***

❖ ***PROPERTIES OF ELECTRO-SENSITIVE HYDROGELS***

Hydrogel reactions can also be induced by electric current acting as an environmental cue. Both pH-sensitive and electric current-sensitive hydrogels are often composed of polyelectrolytes. Hydrogels that are electrosensitive can shrink or swell when an electric field is applied. Hydrogels can occasionally exhibit swelling on one side and edema on the other, which causes the hydrogels to bend. Numerous factors influence the hydrogel's ability to alter form, including swelling, shrinking, and bending. The outcome of applying an electric field to hydrogel may differ from situations in which the hydrogel is submerged in water (or an acetone–water combination) without coming into contact with the electrode if the hydrogel's surface is in contact with the electrode. If electrolytes are present in the aqueous phase, the outcome will still be different. Volume collapse occurs in partially hydrolyzed polyacrylamide hydrogels that come into contact with both the anode and cathode electrodes due to a negligible shift in the electric potential across the gel. It should be mentioned that there are no salts in the hydrogels. Water is lost at the anode side as a result of hydrated H + ions migrating toward the cathode when the voltage is applied. A uniaxial tension is simultaneously produced

along the gel axis, mostly at the anode side, by the electrostatic attraction of negatively charged acrylic acid groups toward the anode surface. The hydrogel shrinks at the anode side as a result of these two concurrent processes.

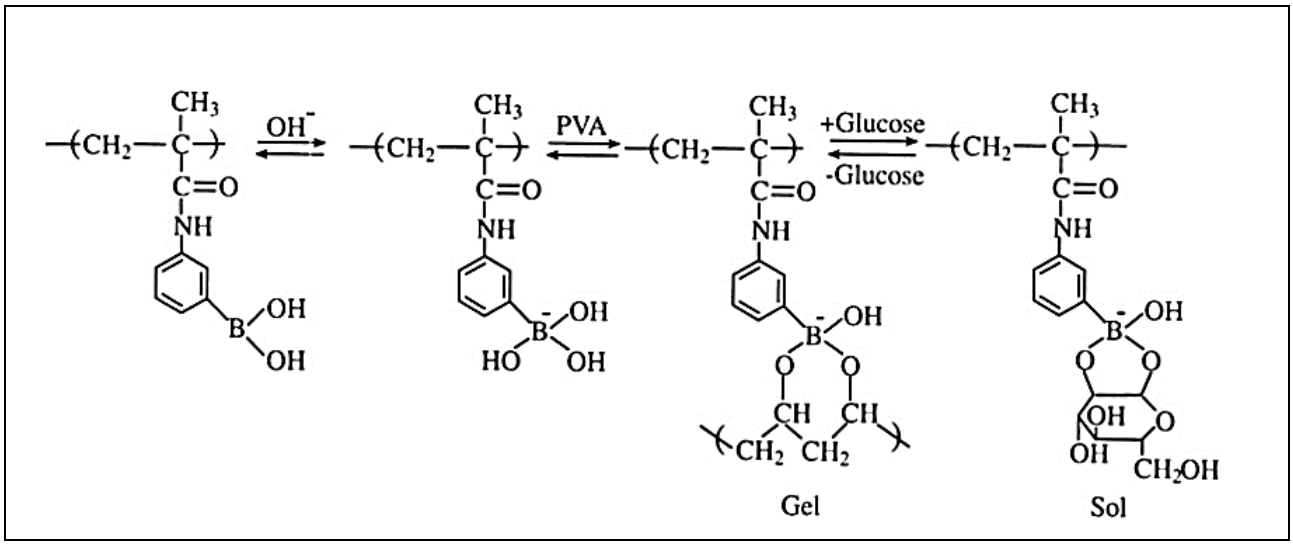

Fig. 7: Sol–gel phase-transition of a phenylborate polymer. At alkaline pH, phenylborate polymer interacts with poly (vinyl alcohol) (PVA) to form a gel. Glucose replaces PVA to induce a transition from the gel to the sol phase.

Source:https://www.google.com/url?sa=i&url=https%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2Fs10971-022-05918-

When an electric field is applied to microspherical hydrogel particles submerged in salt-free water, the hydrogels shrink as a result of electroosmosis (water migration) and electrophoresis (charged ion migration) from the hydrogel to the cathode. By turning the electric field "on" and "off," this characteristic has been utilized for modulated medication delivery. It is impossible to generalize about the swelling/collapse behavior of electrosensitive hydrogels since, as previously said, their reaction is dependent on the experimental setup.

APPLICATIONS OF ELECTRO-SENSITIVE HYDROGELS

❖ *APPLICATIONS IN DRUG DELIVERY*

Controlled medication delivery has made use of electro-sensitive hydrogels. Using electric current, hydrogels composed of poly(2-acrylamido-2-methylpropane sulfonic acid–co-n-butylmethacrylate) were able to pulsatilely release hydrocortisone and edrophonium chloride. Electric stimulation in distilled-deionized water was varied in strength to control the "on-off" release of the medication. An ion exchange between the positively-charged solute and the hydrogen ion created by electrolyzing water was proposed as the explanation for the release pattern of the positively charged medication edrophonium. Pilocarpine and raffinose were delivered pulsatilely using PMA hydrogels that were chemomechanically shrunk and swelled under an electric field. When the electric field was removed, the PAA hydrogel microparticles that had shrunk sharply and quickly when an electric current was applied returned to their initial size. "On–off" release profiles were the outcome of the microparticles' size alterations brought on by the electric field. Poly(dimethylaminopropyl acrylamide) hydrogels with electric field-induced volume variations were employed to release insulin in pulses. Using an electric stimulation, the monolithic device made of sodium alginate and PAA was also utilized to pulsatilely release hydrocortisone. Electric fields have also been utilized to regulate the erosion of hydrogels composed of the poly(ethyloxazoline)–PMA complex in a saline solution, in addition to hydrogel swelling and contraction. Through intermolecular hydrogen bonding between carboxylic and oxazoline groups, the two polymers create a hydrogel. Upon attaching the gel matrix to a cathode surface, the complex disintegrated into water-soluble polymers at the gel surface that faced the cathode when an electric current was applied. By adjusting the applied electrical stimuli, the surface erosion of this polymer system may be regulated either continuously or sequentially. A step function of electric current was used to create pulsatile insulin release.

❖ *APPLICATIONS IN OTHER AREAS*

Chemical energy may be transformed into mechanical energy using electro-sensitive hydrogels, which are essentially pH-sensitive hydrogels. In several applications, such systems can function as artificial muscles or actuators. All living things move by isothermally converting chemical energy into mechanical effort, such as flagellar and ciliary movement and muscle contraction. Using weakly crosslinked poly(2-acrylamido-2-methylpropanesulfonic acid) hydrogels, electrically driven motility has been demonstrated. The

polyanionic hydrogel's surface facing the cathode is coated in surfactant molecules that are positively charged, which lowers the total negative charge. As a result, the hydrogel experiences localized shrinking, which causes it to bend. A worm-like motion might result from the hydrogel rapidly repeating its oscillatory motion when an oscillating electrode polarity is applied.

❖ ***LIMITATIONS AND IMPROVEMENTS***

One benefit of using electro-sensitive hydrogels for drug administration is that the electric field may be readily modulated to regulate the drug release rate. Electro-sensitive hydrogels based on controlled drug delivery are still in their early stages of development. A controllable voltage source is necessary for the use of electro-sensitive hydrogels, in addition to the issue that all hydrogels have, which is their slow response. Furthermore, the majority of electro-sensitive hydrogels function without electrolytes. Creating drug delivery modules based on electrosensitive hydrogels that function in physiological settings might not be simple.

LIGHT-SENSITIVE HYDROGELS

❖ ***PROPERTIES OF LIGHT-SENSITIVE HYDROGELS***

Light-sensitive hydrogels may be used to create opthalmic medication delivery systems, optical switches, and display units. Light-sensitive hydrogels may have unique benefits over others since the light stimulus may be applied instantaneously and precisely in predetermined proportions. For instance, thermal diffusion limits the sensitivity of temperature-sensitive hydrogels, whereas hydrogen ion diffusion may limit the sensitivity of pH-sensitive hydrogels. The creation of light-sensitive hydrogels is crucial for a number of applications in the biological and engineering domains due to their ability to provide the sol-gel stimulus instantly. UV-sensitive and visible light-sensitive hydrogels are two types of light-sensitive hydrogels. Visible light is easily controlled, safe, affordable, and widely accessible, in contrast to UV light. Bis(4-dimethylamino)phenylmethyl leucocyanide, a leuco derivative molecule, was added to the polymer network to create the UV-sensitive hydrogels. Triphenylmethane leuco derivatives are typically neutral, but when exposed to UV light, they split into ion pairs, forming triphenylmethyl cations. When exposed to ultraviolet light, the leucoderivative molecule can ionize, as seen in Fig. 8. The hydrogels responded to UV irradiation by intermittently swelling at room temperature, but they shrunk when the UV light was turned off. A continuous volume phase transition without UV irradiation is not the same as a UV-induced discontinuous volume phase transition. The emergence of cyanide ions created by UV irradiation caused a rise in osmotic pressure within the gel, which in turn caused the swelling caused by UV light. A light-sensitive chromophore, such as trisodium salt of copper chlorophyllin, was added to poly(N-isopropylacrylamide) hydrogels to create visible light-sensitive hydrogels. The "local" temperature of the hydrogel rises when light (such as 488 nm) is introduced because the chromophore absorbs the light and causes it to be locally dissipated as heat through radiationless transitions. Poly(N-isopropylacrylamide) hydrogels are thermosensitive hydrogels whose swelling behavior changes as the temperature rises. The chromophore concentration and light intensity both affect how much the temperature rises. The light-sensitive hydrogels also become sensitive to pH variations when an extra functional group is introduced, such as an ionizable group of PAA Visible light may activate this kind of hydrogel, causing it to shrink, while raising pH can deactivate it, causing it to swell.

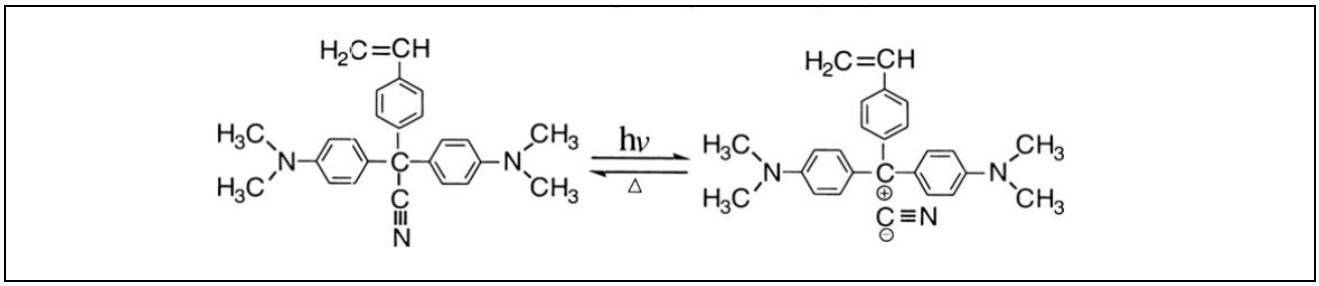

Fig. 8: Structure of leuco derivative molecule bis(4-(dimethylamino)phenyl)(4-vinylphenyl)methylleucocyanide.

Source:https://www.google.com/url?sa=i&url=https%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2Fs10971-022-05918-

In the absence of chromophores, infrared light may also be utilized to elicit a hydrogel response since the visible light-induced volume change of these hydrogels is predicated on the induction of temperature changes via the integrated photosensitive molecules. Water's strong absorption of infrared radiation makes this technique beneficial. The volume phase transition and gel bending toward the laser beam were seen during irradiation of poly(N-isopropylacrylamide) hydrogels devoid of any chromophores using a CO2 laser IR. The CO2 laser intensity determined the amount of bending caused by the temperature differential that formed, whereas the gel's return to its initial shape following irradiation had an exponential pattern.

❖ ***APPLICATIONS***

Photo-responsive artificial muscles, switches, and memory devices may be developed using light-sensitive hydrogels. Based on the reaction of crosslinked hyaluronic acid hydrogels that experience photosensitized breakdown in the presence of methylene blue, the possible use of visible light-responsive hydrogels for temporal drug delivery was also suggested.

❖ ***LIMITATIONS AND IMPROVEMENTS***

Hydrogels nonetheless react slowly to stimuli like light, even though the stimulus's action is immediate. Most of the time, when the temperature changes, the rearrangement of polymer chains must come after the conversion of light into thermal energy. Furthermore, chromophores may leak out during swelling-deswelling cycles unless they are covalently bonded to the polymer backbone.

OTHER STIMULI SENSITIVE HYDROGELS

Other stimuli have also been employed to create environmentally sensitive hydrogels, in addition to the commonly utilized stimuli covered above. Additional stimuli consist of pressure, certain ions, thrombin, and antigen.

❖ ***PRESSURE-SENSITIVE HYDROGELS***

The idea that pressure-induced volume phase transitions in hydrogels are possible originated with thermodynamic calculations based on the theory of uncharged hydrogels. The idea states that hydrogels that collapse under low pressure will expand under increased pressure. This prediction was validated by poly(N-isopropylacrylamide) hydrogel experiments. When the temperature was near its LCST, the degree of swelling of poly (N-isopropylacrylamide) hydrogels rose under hydrostatic pressure. Other hydrogels that demonstrated pressure sensitivity close to their LCSTs were poly(N-n-propylacrylamide), poly(N,N-diethylacrylamide), and poly(N-isopropylacrylamide). One characteristic that seems to be shared by temperature-sensitive gels was their sensitivity to pressure. It was determined that the temperature-sensitive gels' increased LCST value with pressure was the cause of their pressure sensitivity. The sodium iodide concentration affects how positively charged poly (diallyldimethylammonium chloride) hydrogels behave during phase transitions. When the concentration is crucial,

A hydrogel may undergo a collapsed state phase transition when exposed to sodium iodide, but this transition is accompanied by a broad hysteresis. An ion pair and multiplet (ionomer effect) idea was put up to explain these intriguing experimental findings because other salts tested did not cause the network collapse in the investigated concentration ranges.

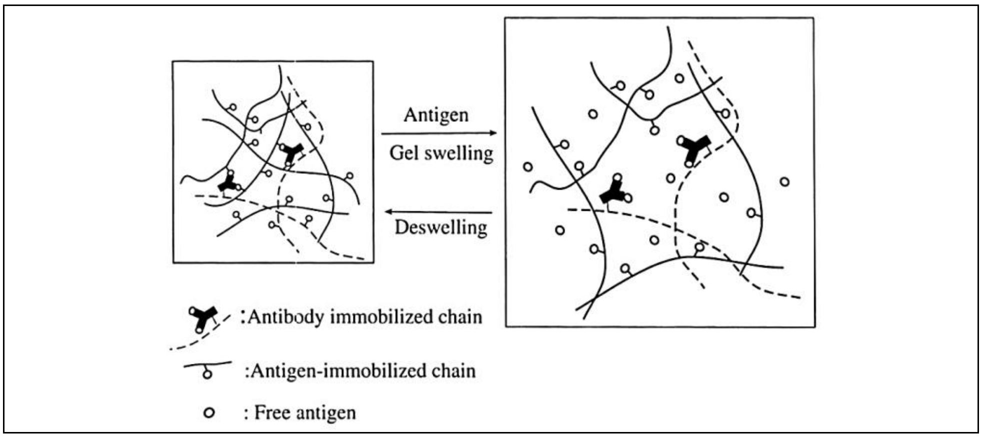

Fig. 9: Swelling of an antigen–antibody semi-IPN hydrogel in response to free antigen.

Source:

❖ ***SPECIFIC ANTIGEN-RESPONSIVE HYDROGELS***

Creating a substance or tool that reacts to particular proteins is very desirable and helpful for several medicinal purposes. Reversible hydrogels in the sol-gel phase were made using antigen-interactions with antibodies. The idea behind glucose-sensitive phase-reversible hydrogels is the same. An antigen and corresponding antibody were grafted onto various polymer networks to create a semi-interpenetrating network hydrogel. Crosslinking interactions that take place during antigen–antibody binding create the gel. The presence of free antigens causes hydrogel swelling, which lowers the crosslinking density by competing with the polymer-bound antigen (Fig. 9).

❖ ***THROMBIN-INDUCED INFECTION-RESPONSIVE HYDROGELS***

PVA hydrogels loaded with grafted gentamycin were created to release antibiotics at the infection site and over time. Gentamycin was chemically bonded to the polymer backbone using peptide linkers, which thrombin may

break down enzymatically. The fact that exudates from the dorsal pouches of rats infected with Pseudomonas aeruginosa had noticeably more thrombin-like enzymatic activity toward a particular peptide sequence than exudates from wounds that were not infected served as the basis for this strategy. This strategy is similar to that of polymeric prodrugs, which release attached drug molecules gradually; the only difference is that infection speeds up the release in this instance. This kind of method can be used on prosthetics, drainage bags, infection-prone catheters, and occlusive wound dressings. Generally speaking, this kind of technology has excellent potential as a stimulus-responsive, controlled drug release mechanism and enough specificity.

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