The Development of An Innovative Intelligent Method Based on Hydrogel

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***Abstract*—Smart hydrogels, which can respond to stimuli and adapt to external inputs, have emerged as an exciting research topic in biomedical engineering. They have proven indispensable in human health care and the pharmaceutical industry because they can selectively release drugs under specific conditions. Intelligent hydrogels, particularly intelligent hydrogels, may detect physiological triggers and deliver drugs at the site of action. To control swelling, hydrogel-based drug delivery systems employ temperature-responsive random copolymers of poly(N-isopropylacrylamide) and poly (vinyl pyrrolidinone). These hydrogels have low critical solution temperatures, which makes them suitable for smart drug delivery applications. Two model drugs, diclofenac sodium and procaine HCl, were trapped within these xerogels. Modulated differential scanning calorimetry, ATR-FTIR, and AFM were used to investigate the effects of medication on xerogels properties. Drug dissolution tests found that higher temperatures caused delayed release. Conventional therapies have limitations that need the use of controlled drug delivery systems. Hydrogel technology has become an essential component of human health care, with the pharmaceutical industry developing cutting-edge hydrogel-based treatments. This review examines the role of polymers and nanocomposite hydrogels. The study developed a constructed drug delivery system (DDS) that can perform a variety of activities, including drug protection, self-regulated oscillatory release, and concentrated unidirectional distribution. Control is achieved by using a pH-sensitive hydrogel and a poly (hydroxyethyl methacrylate) (HEMA) barrier. The device was tested with two model pharmaceuticals, acid orange 8 and bovine serum albumin, and demonstrated targeted unidirectional release in a diffusion cell. The BI layered gate detects variations in environmental pH and generates an oscillating release pattern.**

***Index Terms*—Hydrogels, xerogels, temperature responsive, nanocomposite, pH sensitive.**

I. INTRODUCTION

Wichterle and Lim coined the name "hydrogels" in the 1960s, and their biological applications were proposed. Since then, hydrogel technology has advanced dramatically in the pharmaceutical business. Hydrogels have existed since the evolution of life on Earth, as the name implies. Plant structure, extracellular matrix components, and microbial biofilms are found everywhere; all swelling moieties in nature are evidence of their presence [1]. Polymers are becoming increasingly important in the pharmaceutical business as both drug encapsulants and drug delivery vehicles. Polymers used to delay drug dissolution are intended to slow the rate at which drug molecules are exposed to water in the aqueous environment surrounding the drug delivery system [2]. Chemical or physical crosslinking produces hydrogels, which are a type of polymer that absorbs a large quantity of water while keeping its overall shape. Hydrogels have been extensively researched for drug delivery and biomedical devices in recent decades due to their biocompatibility and ease of control over solute transport [2-4]. Crosslinking the polymeric chains creates a three-dimensional network. Crosslinking can occur through physical interactions, covalent bonding, hydrogen bonding, and van der Wall interactions [2].

Hydrogels, an important class of biomaterials, can be defined as coherent systems composed of a three-dimensional polymer network containing a large number of aqueous phases that cannot dissolve the network through physical and chemical interactions due to the presence of interconnection known as crosslinks [1-3].

Hydrogels are now a popular type of targeted drug delivery system and have been used in a variety of medical and biomedical applications, including cartilage and wound regeneration, bone tissue engineering, biosensors, electronic and soft robotic components, and inflammation relief [4-6].

Smart hydrogels exhibit abrupt changes in their physical properties as well as macroscopic alterations in response to a small external trigger [7]. The nonlinear feedback that these hydrogels provide distinguishes them. Indeed, they can respond to triggers by undergoing a reversible, intensity-scalable, reproducible, and predictable phase volume transformation, as well as returning to their previous shape once the trigger is removed [8-9]. These transitions include physical state changes, solvent interactions, shape and solubility, conductivity, and hydrophilicity [10-11]. Using smart hydrogels in drug delivery systems can reduce dosage frequency, maintain the desired therapeutic concentration in a single dose, and limit side effects by preventing drug buildup in non-target tissues [12-14].

Furthermore, smart hydrogels are easy to prepare and are an excellent choice for extended-release systems including pharmaceuticals. medicine delivery technology can be advanced by combining smart materials into a single constructed device that is responsive to the individual patient's therapeutic needs and capable of delivering a specific dose of medicine in response to a biological state [15]. Such smart therapeutics should have one or more properties, including proper drug protection, local targeting, precisely controlled release, self-regulated therapeutic action, permeation enhancement, enzyme inhibition, imaging, and reporting. The release of medications at specific places has gained a lot of interest recently [16-17]. Depending on the surface receptors, several targeting compounds are used to achieve local targeting. For example, a polymer-drug combination with an antibody can be detected by a cell surface antigen in cancer diagnostics and therapeutics [18].

For peptides or proteins passing through the gastrointestinal (GI) tract, the drug delivery system (DDS) can bind precisely to the mucosal layer or cell surface, increasing drug residence time and bioavailability. Residence time is a significant consideration for medication delivery over the GI tract barrier. Dorkoosh et al. devised a new [19].

DDS for site-specific peptide drug delivery in the intestinal tract with superporous hydrogels (SPH) and SPH composite polymers that swell fast due to gut fluid absorption [20]. As a result, the system became connected to the intestinal wall, allowing for a longer duration of drug release. Shen et al. [21] described an intestinal patch designed for oral delivery. Using a mucoadhesive layer of Carbopol/pectin resulted in a longer residence duration and unidirectional diffusion for improved medication diffusion through the intestinal barrier. Tao et al. used microfabrication techniques and mucoadhesive plant lectins to create microdevices with a long residence time [22–23]. The current study focuses on the development of an assembled DDS capable of integrating numerous functionalities into a single system. Specifically, drug protection and self-regulated oscillatory release were demonstrated utilizing a bilayered self-folding hydrogel design. Poly (hydroxyethyl methacrylate (poly (HEMA)) coated with a poly (ethylene oxide)/poly (propylene oxide)/poly (ethylene oxide) (PEO - PPO -PEO) surfactant was used to improve mucoadhesion on the device surface for targeted unidirectional release [23-24]. The release patterns of two model medicines, acid orange 8 (AO8) and bovine serum albumin (BSA), were investigated in this built system. The results were compared to standard hydrogels containing medicines and enteric coating methods [24].

II. CLASSIFICATION OF HYDROGELS

The structure of hydrogels, the mechanism of synthesis, and the types of crosslinks are all essential parameters used to classify them. The discrepancies in properties are the result of variations in any of the listed qualities. First, based on the route of their synthesis, they can be classed as:

Homopolymer hydrogels (consisting of only one type of hydrophilic monomer) Copolymer hydrogels or network gels are formed of two types of monomers. Multi polymer hydrogels (composed of three types of monomers or an interpenetrating polymeric network). Second, the other form of classification is based on the type of ionic charges contained in polymer networks: Anionic hydrogels are thermos associative carboxymethyl pullulan hydrogels. Cationic hydrogels (new thermosensitive cationic hydrogels of NIPAM and AAPTAC) [25-26].

Neutral hydrogels (miscible blends of water-insoluble polymers such as poly (2,4,4-trimethylhexamethylene terephthalamide). 6. Ampholytic hydrogels (acrylamide-based hydrogels). Third, hydrogels can be classed according to their physical structures: Amorphous hydrogels (chains organized randomly). Semi-crystalline hydrogels (dense sections with organized macromolecular arrangement) 9 Hydrogen bound or complexation structures (three-dimensional networks generated by hydrogen bonds) [26-27].

III. EMERGENCE OF HYDROGELS AS DRUG DELIVERY SYSTEM

The term smart polymers derive from hydrogels' ability to mimic the non-linear response of DNA and proteins. Above all, hydrogels' ability to adapt structural changes in response to various physical or chemical triggers (Figure 3) makes them ideal candidates for drug delivery systems. The existing medication delivery techniques are deplorable, ineffectual, and intrusive [27–28]. The discovery of Micro/Nano Hydrogels provided a perceptive method of sustained drug delivery systems that overcame the aforementioned challenges. Furthermore, drug release kinetics can be resolved by adjusting the form, size, and drug dispersion of the hydrogels during the assembly process [28]. The smart hydrogels filled with cancer medications resulted in a prolonged release of the pharmaceuticals until they reached the cancer cells. These systems have considerable potential as a safe and effective carrier for future medications with better mechanisms [28].

IV. BIODEGRADABLE AND PH RESPONSIVE HYDROGELS

Advances in polymer science have resulted in the development of effective and smart biodegradable polymeric hydrogels capable of self-regulating drug delivery in response to a specific stimulus. The degradability can be broadly separated into two categories: (i) physical damage, also known as erosion of polymers, which is based on the dissolution and diffusion process, and (ii) chemical degradation [29].
The biodegradability of polymers can be enhanced by including labile groups such as ester, ortho ester, anhydride, carbonate, amide, urea, and urethane into their backbone. The capacity of hydrogels to respond to external stimuli, particularly pH fluctuation, is one of their most valued properties, making them attractive candidates for application in drug delivery systems [29-30]. The mechanism can be explained in simple terms. Hydrogels are known to be swelling ionic networks with acid or basic attached groups that can ionize and develop a fixed charge on the polymer matrix. All ionic materials have pH and ionic strength sensitivity. The swelling force actually dominates non-ionic materials, which are the result of fixed charge localization on the pendant groups. As a result, a little shift in pH in the environment causes a significant change in the network's total mesh size [30].
Figure 1 depicts the swelling and de-swelling of hydrogel networks as the temperature and pH change. The pH responsive nature of hydrogels has been widely explored for drug delivery applications. The structure of the polymeric matrix influences its pH responsive properties. The attached acidic carboxylic and sulphonic acids, as well as basic functional groups such as ammonium salts, operate as proton acceptors or donors as the pH changes [31–32].

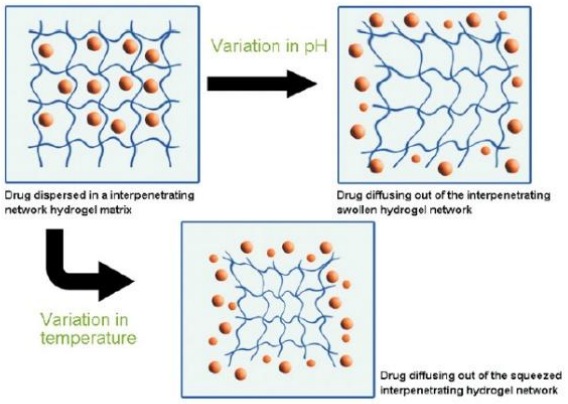

Fig. 1: Swelling and deswelling behaviour of interpenetrating hydrogel network with the variation in temperature and pH

V. SMART POLYMERS USED FOR HYDROGEL-BASED DRUG DELIVERY SYSTEMS

➢ Poly (lactic –glycolic acid)

The anionic polymerization of this cyclic lactide monomer occurred in the early 1960s. Kulkarni et al. (16) were the first to employ this polymer in medicine. The scientists discovered that implantation of these polymers in guinea pigs and rats had no negative effects, but that the polymer hydrogel matrix degraded with time [33]. Thus, lactic and glycolic acid copolymers are frequently used for the controlled

release of pharmacological excipients. Langer and Vacant (1993) were pioneers in developing these polymers as porous scaffolds for tissue engineering. The food and drug administration (FDA) has approved this emerging copolymer for use in biomedical applications due to its biocompatibility and biodegradability. This copolymer has a glass transition temperature of 40-60 ºC, unlike polylactide and polyglycolide, which have low solubility. Thus, this makes it a perfect candidate to be used in the manufacture of various heat sensitive hydrogels [34-35].

➢ Hydroxyethyl cellulose

Hydroxyethyl cellulose is an essential cellulose derivative used in medication administration. HEC's highlighting properties, such as water solubility, non-ionic form, thickening agent, ability to form suspension and emulsion adhesion, film formation and dispersion, water retention, and protection, make it a suitable candidate for use in the synthesis of hydrogels used for drug delivery [36]. HEC has double the water retention of methyl cellulose and hydroxypropyl cellulose, as well as the highest collision protection. This section discusses recent advances in hydroxyethyl cellulose-based hydrogel manufacturing. The glucose repeat unit is substituted by hydroxyethyl ether. These are the favourable groups that prevent the polymer from crystallizing and, when added to a solution, make it soluble. To begin, nanocomposite hydrogels made by conjugating HEC with other polymers via physical or chemical mixing are explored, as is the development of temperature responsive hydrogels based on it and its derivatives, as well as their applications. Gorgieva et al. created a unique hydrogel with dual responsive absorption properties by combining HEC and carboxymethyl cellulose in an aqueous solution and using citric acid (CA) as a cross-linker [37].

There have been efforts to produce hydrogel membranes for wounds utilizing HEC. Researchers are focusing on developing translucent membranes that allow wounds to be observed during dressing changes without affecting the healing process. This discovery created hydrogels that can be manufactured from fabrics made of woven or nonwoven gel-forming fibers. When these reinforcing materials absorb exudates, they become transparent or translucent, allowing for easy sight of the wound. The sheet is composed of hydrogel polymer [38-40]. This invention does not require the removal of the dressing. Specifically, cellulose derivatives, which are gel-forming fibers with absorbency of between 10g/g of sodium/calcium chloride, are employed. Many vaginal microbicide formulations use HEC as an inactive component. These microbicides are intended to prevent the spread of sexually transmitted diseases like HIV. This polymer has been investigated for use as a placebo gel in HIV microbicide experiments. Its use as a universal placebo in HIV microbicide trials has been adopted, and its safety is being investigated [41-42].

Starch

Hydrogels based on starch as a base or modifying material represent a great choice in tissue engineering, drug delivery, and other biomedical applications. Recently, Lima et al.27 developed a stimuli responsive injectable hydrogel of chitosan – starch. The research group encapsulated the chitosan – starch-based gels derived stromal cells for the regeneration of articular cartilage. The incorporation of the starch gave the gels a firm textured gel, giving them the desired mechanical strength. The degradation profile of the gels was also improved. Thus, it was found that these chitosan ²- glycerophosphate-starch hydrogels can be used for chondrogenic differentiation of ADSC for cartilage regeneration. Starch hydrogels have found their use in wound dressing. Pal et al.28 attempted to prepare transparent starch-based hydrogel membranes by cross linking of polyvinyl alcohol with heat treated corn starch suspension [44-45].

Nanocomposite hydrogels

A Nano composite hydrogel is a three-dimensional water-swollen network that is cross-linked and contains nanoparticles. The network is formed through physical and chemical interactions. The incorporation of nanoparticles in the hydrogel matrix enhances the hydrogel's unique physicochemical properties such as mechanical, optical, thermal, barrier, acoustic, and electric simulations [45].

Nanocomposite based on inorganic and magnetic nanoparticles

Nanoparticles, which are neither charged nor stabilized, demonstrate the ability to aggregate. Exfoliation in water may occur for charged nanoparticles, such as silicates, due to colloidal

interactions that stabilize the gel. To build a stable hydrogel nanocomposite, the dispersion of these nanoparticles must be homogeneous, and the creation of large-scale structures must be regulated [45]. Thus, the addition of silicates to poly (ethylene oxide) and poly(acrylamide) matrices acts as a cross-linking agent and improves network strength. Researchers discovered that hydrogen bonding, ionic, dipole, and other interactions, such as polymer entanglements, all play a role in normal cross linking. A substantial body of research, including current reviews, discusses the synthesis, characterisation, and uses of polymer nanocomposite hydrogels containing inorganic and magnetic nanoparticles. Nanoparticles can also act as crosslinking (physical and chemical) agents. Polymer-magnetic nanocomposites containing particles in the polymer matrix (dispersed throughout and/or cross-linking polymer chains) can be employed to release pharmaceuticals remotely [45–46].

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