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STIMULI SENSITIVE HYDROGELS IN DRUG DELIVERY SYSTEMS

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ABSTRACT

Hydrogels are the 3 dimensional cross linked polymeric networks which absorb the water 10-20 times of its molecular weight. Hydrogels are sensitive to different environmental stimuli like pH, temperature, ion, electric signals, light, pressure, antigen specific, enzyme sensitive, and glucose levels. When the environment is get change they get swell, and swelling is the most important characteristics for release of drug through hydrogel devices, and release by either diffusion or swelling or chemically controlled. These stimuli sensitive hydrogel used in delivery of drug through various routs like oral, ophthalmic parenteral drug, nasal TDDS, and also in novel drug delivery like in nanoparticles. Now a day's stimuli sensitive hydrogels are also used in administration of DNA. Most widely stimuli sensitive hydrogels used are pH and temperature sensitive hydrogels because in body wide pH range available so it is used for targeted drug delivery. Hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as biosensors as well as drug delivery systems.

INTRODUCTION: Hydrogels are a network of hydrophilic polymers that can swell in water and hold a large amount of water while maintaining the structure [1]. Approaches of dosage form designs require a carrier which should be biocompatible and biosensitive like hydrogels [2]. A three-dimensional network was formed by cross linking polymer chains[1]. The cross- linking renders these structures insoluble in water due to anionic interaction and hydrogen–bonding. These structures imbibe water or biological fluids in large amount at least 10-20 times of their molecular weight, thus become swollen [2]. Drug release in response to external stimuli, and are most investigated. Hydrogels having such 'sensor' properties can undergo reversible volume phase transitions or sol-gel phase transitions upon changes in the environmental condition such stimuli and response are shown in **fig. 1**.

These properties of polymers play important role in drug delivery [3]. Hydrogel-based drug delivery devices have become a major area of research interest Hydrogels can protect drugs from hostile environments, e.g. the presence of enzymes and low pH in the stomach. Their porosity permits loading of drugs into the gel matrix and subsequent drug release at a pre-designed rate [3].

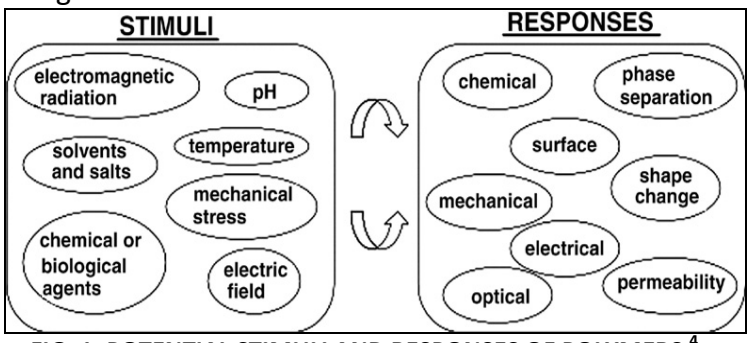

FIG. 1: POTENTIAL STIMULI AND RESPONSES OF POLYMERS [4]

Preparation of Hydrogels: Block diagram for preparations of hydrogels shown in **fig. 2**.

1. **Use of Cross Linkers**: Copolymerization of monomers using multifunctional co-monomer, which acts as cross linking agent, initiator initiates the polymerization reaction which can be carried out in bulk, solution or suspension. So hydrogels prepared by Suspension, emulsion, precipitation, bulk, or interfacial polymerization reaction. Monomers used here contain an ionizable group that can be ionized or can undergo a substitution reaction after the polymerization completed. Thus, the hydrogels synthesized may contain weakly acidic groups like carboxylic acids or weakly basic groups like substituted amines or a strong acidic and basic group like sulfonic acid and quaternary ammonium compounds. Crosslinking is done by use of chemicals or irradiation. Cross linkers used are glutaraldehyde, calcium chloride and oxidized konjac glucomannan (DAK) [9].

2. **Isostatic Ultra High Pressure (IUHP):** Polymerization is done by subjecting monomer to ultra high pressure at constant temperature. Suspension of natural biopolymers (eg.-starch) are subjected to ultra high pressure of 300-700 MPa for 5 to 20 minutes in a chamber which brings about changes in the morphology of the polymer i.e. gelatinization of starch molecules occur. Temperature in the chamber varies from 40 to 52^{o}C [9].

3. **Use of Nucleophilic substitution reaction:** Nuclrophilic group are electron rich center so they used for preparing hydrogels. A pH and temperature sensitive hydrogel viz. hydrogel of N-2-dimethylamino ethylmethacrylamide (DMAEMA) has been prepared using nucleophilic substitution reaction between methacyloyl chloride and 2-dimethylamino ethylamine [2].

4. **Use of Gelling Agent:** Eg., glycophosphate1-2propanediol, glycerol, trehalose, mannitol etc used in the preparation of hydrogels. Usually the problem of turbidity and presence of negative charged moieties which are associated with this method pose problem of interaction with the drug [2].

5. **Use of irradiation:** Irradiation method is suitable as well as convenient but the processing is costly along with the poor mechanical strength of the product [10]. High energy radiation like gamma and electron beam has been used to prepare the hydrogels. The irradiation of aqueous polymer solution results in the formation of radicals on the polymer chains, resulting in the formation of macroradicals. Recombination of macroradicals on different chains results in the formation of covalent bonds, and finally a cross linked structure is formed [2].

6. **Freeze Thawing:** Freeze thawing method imparts sufficient mechanical strength and stability to the hydrogels except that they are opaque in appearance with little swelling capacity [7, 10]. S. Mohammad *et al*., prepared freeze-thawed PVA/kaolinite nanocomposite hydrogels. Freeze-thawed nanocomposite hydrogels were prepared on the basis of polyvinyl alcohol (PVA) containing 0, 5, 10, and 15 wt% of kaolinite (based on the dried hydrogel).

   The micro-structure of nanocomposite was investigated using the X-ray diffractometry (XRD) and transmission electron microscopy (TEM) techniques. Intercalated morphology was observed for all prepared nanocomposite hydrogels. The effect of kaolinite on the mechanical properties of PVA/kaolinite nanocomposite hydrogels was studied using uniaxial tensile test (ASTM D-1822-99), dynamic mechanical thermal analysis (DMTA), and hardness measurement.

   Remarkable increases on the tensile modulus and tensile strength were observed for the nanocomposite hydrogels, e.g. 228 and 131% increases were achieved in tensile modulus and tensile strength by incorporating 15% wt of kaolinite into PVA hydrogel, respectively. The DMTA test was performed in the compression mode, using disc-shaped samples with a diameter of 11 mm and a thickness of 5 mm. It was shown that the storage modulus of PVA hydrogel increases by increasing the kaolinite content.

The storage modulus of nanocomposite hydrogel containing 15% wt of kaolinite in the regions below and above 0°C were on average 210 and 140% higher than of pure PVA hydrogel, respectively. The results also showed that the hardness is directly depended to the quantity of kaolinite added to the nanocomposite hydrogel [21].

7. **Use of water and critical conditions of drying:** Aerogels of carbon have been prepared by super critically controlling the drying conditions.eg: Aerogels of resorcinol formaldehyde hydrogels. The method is expensive but leads to formation of xerogels with good mechanical strength [10].

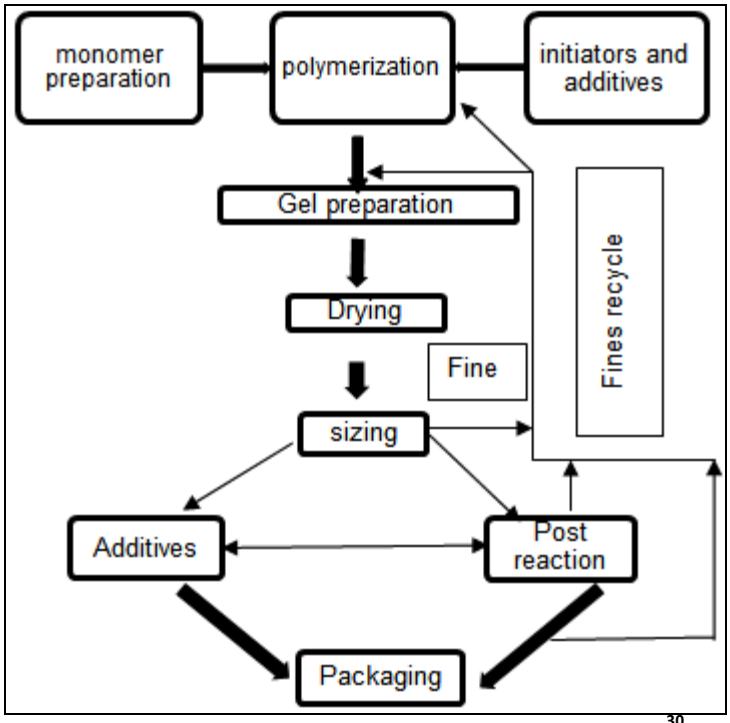

FIG. 2: HYDROGEL PREPARATION BLOCK DIAGRAM [30]

Morphological characterization: Hydrogels were characterized for morphology which analyzed by equipment like stereomicroscope.

1. **X-ray Diffraction:** It is used to understand whether the polymers retain their crystalline structure or they get deformed during the processing.

2. ***In-vitro* release study for Drugs:** Since hydrogels are the swollen polymeric networks, interior of which is occupied by drug molecules, therefore, release studies are carried out to understand the mechanism of release over a period of application [11].

3. **FTIR (Fourier Transform Infrared Spectroscopy):** Any change in the morphology of hydrogels changes their IR absorption spectra due to stretching and O-H vibration. Formation of coil or helix which is indicative of cross linking is evident by appearance of bonds near 1648cm^{-1}. The stretching or bending vibrations are basically responsible for the changes in IR absorption spectra [10]. Dry the hydrogels and scanned from 650 to 4000 cm^{-1} at the reflex mode for their extremely thin and transparent characters [11].

4. **Swelling behavior:** The hydrogels are allowed to immerse in aqueous medium or medium of specific pH to know the swellability of these polymeric networks. These polymers show increase in dimensions related to swelling. The hydrogels swell in water to form the polymeric network. The formation of this polymeric network is responsible for the morphological characterization of drug.

   Polymers are characterized by viscosity method, osmometry, light scattering and size exclusion chromatography [2].

Water content of hydrogel is affected by;

i. Nature of monomer

ii. Type and density of cross-links

iii. Other factor-temperature, pH, ionic strength.

$$\textbf{Swelling ratio= } r = (w_1 - w_0)\,/w_0$$

Where, w_1 =weight after swelling; w_2= weight before swelling

5. **Rheology:** Hydrogels are evaluated for viscosity under constant temperature of usually 4°C by using Cone Plate type viscometer [2, 10].

The stimuli that induce various responses of the Hydrogel Systems are as follows:

1. pH sensitive hydrogels
2. Temperature sensitive hydrogels
   a. Ion sensitive hydrogels

b. Light sensitive hydrogels

c. Enzyme sensitive hydrogels

d. Glucose sensitive hydrogels

e. Pressure-sensitive hydrogels

f. Specific antigen-responsive hydrogels

g. Electric signal sensitive hydrogels

h. magnetic field sensitive hydrogels

1. **pH sensitive Hydrogels:** All the pH-sensitive polymers contain pendant acidic (e.g. carboxylic and sulfonic acids) or basic (e.g. ammonium salts) groups that either accept or release protons in response to changes in environmental pH [1]. pH in various tissues and cellular compartments shown in **table 1**.

TABLE 1: pH IN VARIOUS TISSUES AND CELLULAR COMPARTMENTS [4]

Tissue/cellular compartment	pH
Blood	7.35–7.45
Stomach	1.0–3.0
Duodenum	4.8–8.2
Colon	7.0–7.5
Early endosome	6.0–6.5
Late endosome	5.0–6.0
Lysosome	4.5–5.0
Golgi	6.4
Tumour, extracellular	7.2–6.5

pH sensitive hydrogels used to encapsulate proteins in acrylamide polymer cross-linked with bisacrylamide acetal cross linkers.

At pH 5, the pore size of the acetal cross-linked hydrogels increases leading to release of protein and at neutral pH, the acetal groups remain intact as cross linkers and protein do not diffuse out easily. Eg: polymethylmethacrylate (PMMA), poly-acrylamide (PAAm), polyacrylic acid (PAA), poly dimethylaminoethylmethacrylate (PDEAEMA) and polyethylene glycol as shown in **fig. 4** [2].

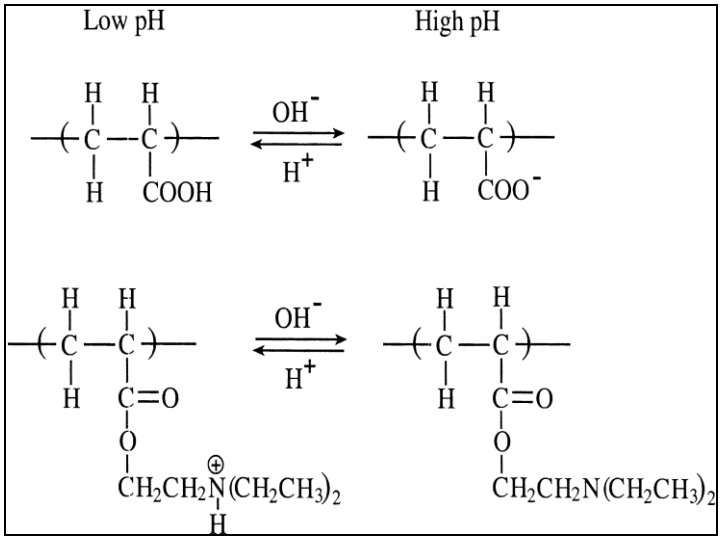

FIG. 3: pH-DEPENDENT IONIZATION OF POLYELECTROLYTES. POLY (ACRYLIC ACID) (TOP) AND POLY (*N*, *N*9-DIETHYLAMINOETHYL METHACRYLATE) (BOTTOM) [1]

2. **Temperature sensitive Hydrogels:** Many polymers exhibit a temperature-responsive phase transition property. The structures, LCST AND UCST of some of those polymers are shown in **fig. 4 and table 2** respectively.

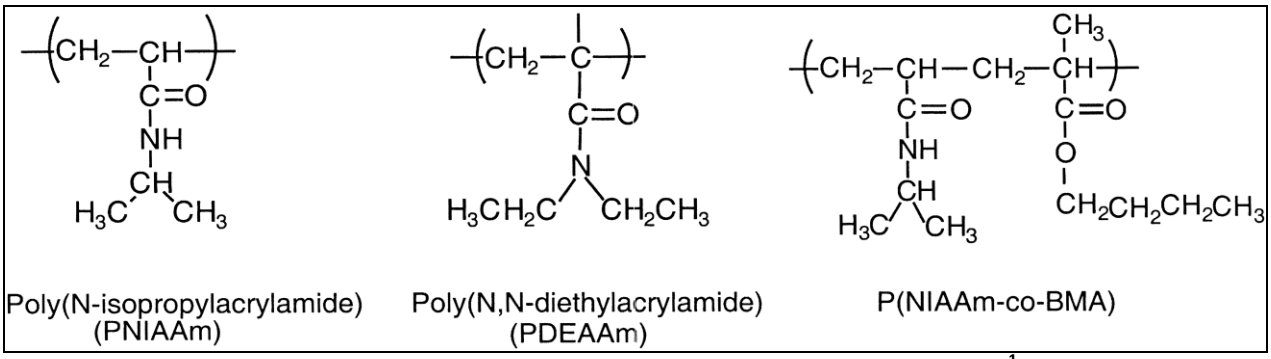

FIG. 4: STRUCTURES OF SOME TEMPERATURE-SENSITIVE POLYMERS [1]

A positive temperature-sensitive hydrogel has an upper critical solution temperature (UCST), they contracts upon cooling below the UCST. Eg: poly (acrylic acid) (PAA), polyacrylamide (PAAm) Polymers increase their water-solubility as the temperature increases.

Polymers with LCST decrease their water-solubility as the temperature increases due to shrinking. This behavior is known as inverse (or negative) temperature-dependence. These hydrogels are made of polymer chains that either possess moderately hydrophobic groups or contain mixture of hydrophilic and hydrophobic segments [1, 2].

3. **Ion sensitive Hydrogels:** Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion-sensitive ones. While k-carrageenan forms rigid, brittle gels in reply of small amount of K^+, i-carrageenan forms elastic gels mainly in the presence of Ca^{+2}.

TABLE 2: LCST AND UCST OF SEVERAL TYPICAL THERMOSENSITIVE POLYMERS

Polymer	LCST ^oC
Poly(*N*-isopropylacrylamide) (PNIPAM)	32
Poly(*N,N*-diethylacrylamide) (PDEAM)	25
Poly(*N*-ethylmethacrylamide) (PNEMAM)	58
Poly(methyl vinyl ether) (PMVE)	34
Polymer	UCST ^oC
PAAm / PAAc IPN	25

Gellan gum commercially available as Gelrite is an anionic polysaccharide that undergoes in situ gelling in the presence of mono- and divalent cations, including Ca^{2+}, Mg^{2+}, K^+ and Na^+. Gelation of the low methoxy pectins can be caused by divalent cations, especially Ca^{2+}.Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations e.g. Ca^{2+} due to the interaction with gulcouronic acid blocks in alginate chains [12]. Nonionic poly(*N*-iso propylacryl amide) hydrogel, however, showed a sharp volume phase transition at a critical concentration of sodium chloride in aqueous solution. The phase transition behavior of positively charged poly (diallyldimethyl ammonium chloride) hydrogels is sensitive to the concentration of sodium iodide [1].

4. **Light sensitive Hydrogels:** Light-sensitive hydrogels have potential applications in developing optical switches, display units, and ophthalmic drug delivery devices. Since the light stimulus can be imposed instantly and delivered in specific amounts with high accuracy [1].

   a. **The UV-sensitive Hydrogels**: Synthesized by introducing a leuco derivative molecule, bis (4-dimethylamino) phenyl methyl leucocyanide, into the polymer network. The leuco derivative molecule can be ionized upon ultraviolet irradiation. At a fixed temperature, the hydrogels discontinuously swelled in response to UV irradiation but shrank when the UV light was removed. The UV light-induced swelling was due to an increase in osmotic pressure within the gel due to the appearance of cyanide ions formed by UV irradiation [1, 3].

   b. **Visible light-sensitive Hydrogels:** Prepared by introducing a light-sensitive chromophore (e.g. trisodium salt of copper chlorophyllin) to poly (N-isopropyl acrylamide) hydrogels. When light (e.g. 488 nm) is applied to the hydrogel, the chromophore absorbs light which is then converted in to heat. The temperature increase alters the swelling behavior of poly (N-isopropyl acrylamide) hydrogels, which are thermo sensitive hydrogels. The temperature increase is proportional to the light intensity and the chromophore concentration [1, 3].

5. **Enzyme sensitive Hydrogels:** Some enzymes are used as important signals for diagnosis to monitor several physiological changes, and specific enzymes in specific organs have become useful signals for site specific drug delivery. The microbial enzymes that are predominantly present in the colon can be used as signals for site-specific delivery of drugs to the colon [13]. Hovgaard *et al.,* focused on the fact that microbial enzymes in the colon, such as dextranase, can degrade the polysaccharide dextran. They prepared dextran hydrogels cross-linked with diisocyanate for colon-specific drug delivery.

   The dextran hydrogels were degraded in vitro by a model dextranase, as well as in vivo in rats and in a human colonic fermentation model. Release of a drug from the dextran hydrogels can be controlled by the presence of dextranase. Drug release from the dextran hydrogels in the absence of dextranase was observed to be based on simple diffusion processes, however in the presence of dextranase it was mainly governed by the degradation of the

dextran. Thus hold promise as intelligent systems for colon-specific drug delivery [22]. Yui *et al*., prepared dual stimuli-sensitive hydrogels that can be degraded in the presence of two enzymes as biological stimuli shown in **fig. 5**. The dual-stimuli-sensitive hydrogels consisted of interpenetrating polymer networks (IPNs) of oligo peptide-terminated poly (ethylene glycol) (PEG) and dextran. Only the presence of both papain and dextranase could induce the degradation of the IPN hydrogels, while the presence of only one of the two enzymes was ineffective [23, 24].

6. **Glucose sensitive Hydrogels:** Glucose-sensitive hydrogels are very useful for the development of self-regulated insulin delivery systems and enable us to construct an artificial pancreas that can administer the necessary amount of insulin in response to the blood glucose concentration. The following subsections focus on three types of glucose-sensitive hydrogels.

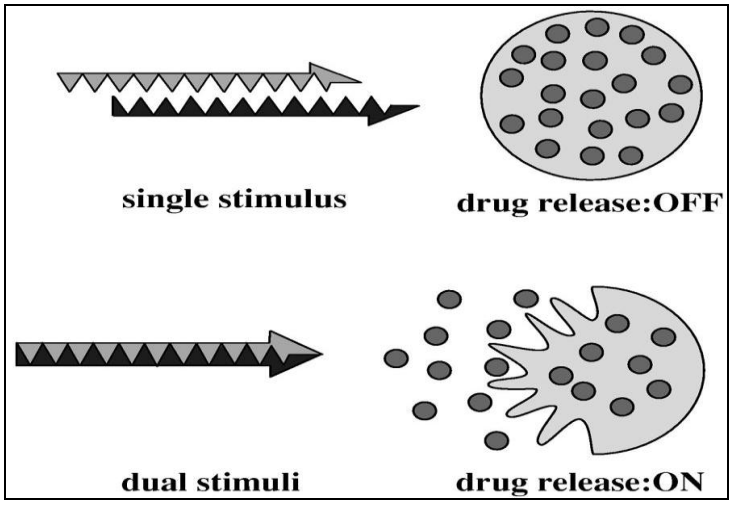

FIG. 5: CONCEPT OF DUAL-STIMULI-SENSITIVE DRUG RELEASE BY IPN STRUCTURED HYDROGEL [13]

a. **Glucose Oxidase-Loaded Hydrogels:** Glucose oxidase with pH-sensitive hydrogels is used to sense glucose and regulate insulin release. This method is used by many researchers to develop glucose-sensitive insulin delivery systems. Glucose is converted to gluconic acid by glucose oxidase, thus lowering the pH in the hydrogels. Insulin can be released by the pH-sensitive swelling of the hydrogels diagrammatically shown in **fig. 7** [14].

b. **Lectin-loaded Hydrogels:** Lectins, which are carbohydrate-binding proteins, interact with glycoproteins and glycolipids on the cell surface and induce various effects, such as cell agglutination, cell adhesion to surfaces, and hormone-like action. The unique carbohydrate-binding properties of lectins are very useful for the fabrication of glucose-sensitive systems. Brownlee *et al.,* and Kim *et al*., were pioneers in the development of glucose-sensitive insulin release systems using (concanavalin A) Con A. Their strategy was to synthesize a stable, biologically active glycosylated insulin derivative able to form a complex with Con A. The glycosylated insulin derivative could be released from its complex with Con A in the presence of free glucose, based on the competitive and complementary binding properties of glycosylated insulin and glucose to Con A [25].

c. **Hydrogels with Phenyl Boronic Acid Moieties**: The preparation of glucose-sensitive hydrogels without biological components such as proteins, but instead of complex formation between a phenyl boronic acid group and glucose, Phenyl boronic acid and its derivatives form complexes with polyol compounds, such as glucose in aqueous solution. The complex between phenyl boronic acid and a polyol compound can be dissociated in the presence of a competing polyol compound which is able to form a stronger complex [1, 3, 13, 14].

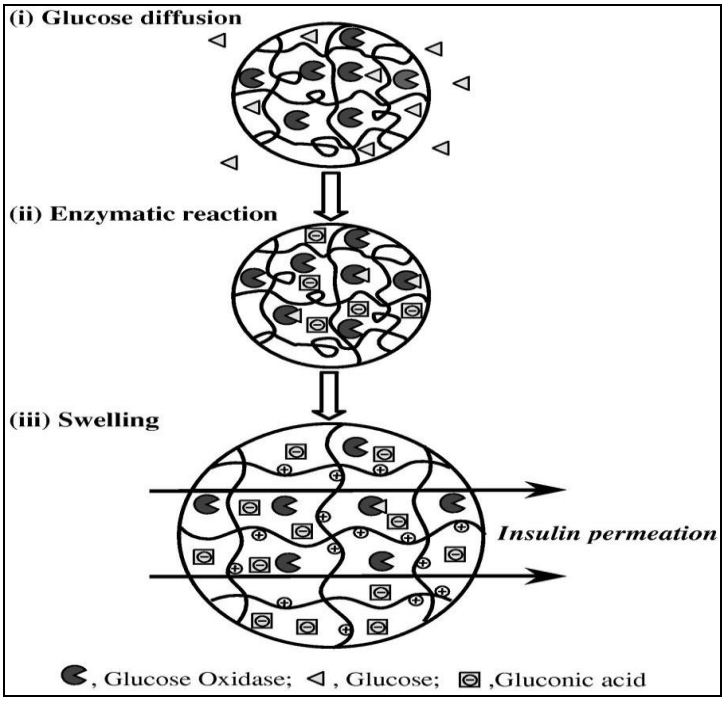

FIG. 6: SCHEMATIC REPRESENTATION OF THE GLUCOSE-SENSITIVE HYDROGEL MEMBRANE CONSISTING OF A POLY (AMINE) AND GLUCOSE-OXIDASE-LOADED MEMBRANE

7. **Pressure-sensitive Hydrogels:** Hydrogels which collapsed at low pressure would expand at higher pressure. Experiments with poly (N-isopropyl acrylamide) hydrogels confirmed this prediction. The degree of swelling of poly (N-isopropyl acrylamide) hydrogels increased under hydrostatic pressure when the temperature is close to its LCST. Eg: poly (N-n-propyl acrylamide), poly (N, N-diethyl acrylamide) and poly (N-isopropyl acrylamide).The pressure sensitivity appeared to be a common characteristic of temperature-sensitive gels. It was concluded that the pressure sensitivity of the temperature-sensitive gels was due to an increase in their LCST value with pressure [1, 2, 13].

8. **Specific Antigen-Responsive Hydrogels:** The specific antigen-recognition function of an antibody can provide the basis for constructing sensors with various uses for immunoassays and antigen sensing. This section describes novel antigen-sensitive hydro-gels that undergo swelling changes in response to a specific antigen asshown in **fig. 7**. Antigen-sensitive hydrogels were prepared by using antigen–antibody bonds at cross-linking points in the hydrogels. For example, rabbit immunoglobulin G (IgG), the antigen, was chemically modified by coupling it with N-succinimidyl acrylate (NSA) in phosphate buffer solution to introduce vinyl groups into the rabbit IgG. The resultant vinyl-rabbit IgG was mixed with the antibody, goat anti rabbit IgG (GAR IgG), to form an antigen–antibody complex. The vinyl-rabbit IgG was then copolymerized with acrylamide (AAm) as a comonomer and N,N9-methylenebisacrylamide (MBAA) as a cross-linker in the presence of GAR IgG, resulting in a hydrogel containing antigen–antibody bond sites (antigen–antibody entrapment hydrogel) [13].

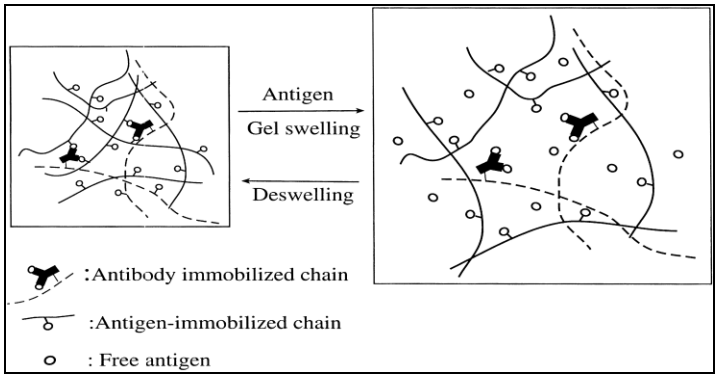

FIG. 7: SWELLING OF AN ANTIGEN–ANTIBODY SEMI-IPN HYDROGEL IN RESPONSE TO FREE ANTIGEN

9. **Electric signal sensitive Hydrogels:** Hydrogels sensitive to electric current are usually made of polyelectrolyte's such as the pH-sensitive hydrogels. Electro-sensitive hydrogels undergo shrinking or swelling in the presence of an applied electric field. Sometimes, the hydrogels show swelling on one side and deswelling on the other side, resulting in bending of the hydrogels [1, 15]. The hydrogel shape change (including swelling, shrinking and bending) depends on a number of conditions. Chondroitin 4-sulphate hydrogels were examined by Jensen *et al*., as potential matrices for the electro-controlled delivery of peptides and proteins [26].

10. **Magnetic Field sensitive Hydrogels:** External stimuli like magnetic field can be used as externally actuated drug delivery systems and in microfluidic devices. Langer *et al*., launched the concept of using external magnetic fields to achieve pulsatile release from polymer composites [27]. They demonstrated an externally controlled on demand insulin release from magnetic composite of ethylene vinyl acetate by application of low frequency oscillating magnetic field. S. Satarkar *et al.,* prepared Magnetic hydrogel nanocomposites for remote controlled pulsatile drug release [28]. A high frequency alternating magnetic field (AMF) was used to trigger the on-demand pulsatile drug release from the nanocomposites. These synthesized by incorporation of superparamagnetic Fe_3O_4 particles in negative temperature sensitive poly (N-isopropylacrylamide) hydrogels. Application of AMF resulted in uniform heating within the nanocomposites leading to accelerated collapse and squeezing out large amounts of imbibed drug release at a faster rateas shown in **fig. 8** [16].

11. **Drug Release mechanisms from Hydrogel Devices:** Hydrogels imbibe more water than 90% of their weight due to hydrophilicity, thus differing in their release mechanisms from hydrophobic polymers. Various models have been developed to predict the release of an active agent from a hydrogel device as a function of time. These are divided into three categories and their mechanism shown in **fig. 10**.
    1. Diffusion controlled
    2. Swelling controlled
    3. Chemically controlled

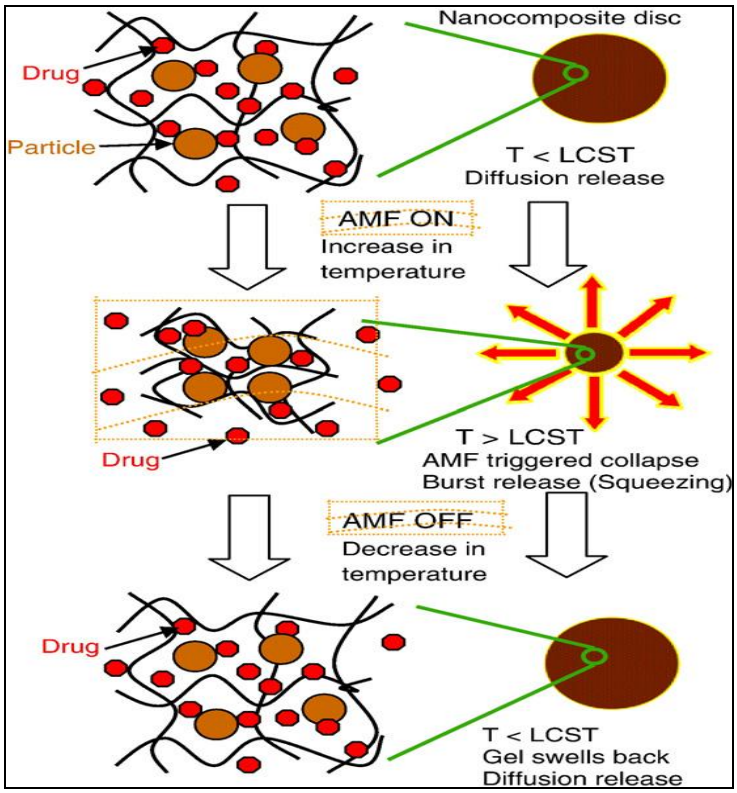

FIG. 8: SCHEMATIC SHOWING THE EFFECT OF ON–OFF CYCLES OF AMF TO THE MAGNETIC NANOCOMPOSITES OF NIPAAM. IT SHOWS THE AMF TRIGGERED COLLAPSE AND RESULTANT BURST RELEASE DUE TO SQUEEZING EFFECT [16]

1. **Diffusion Controlled:** It is most widely applicable mechanism related to drug release. Fick's law of diffusion is commonly used in modeling of this release. Types of diffusion - controlled hydrogel delivery systems are as follows

   a. Reservoir system

   b. Matrix system

   For reservoir system drug depot is surrounded by a polymeric hydrogel membrane. Fick's first law describes drug release through the membrane. Where Flux of the drug/ drug corresponding to the mass average velocity of the system [2, 7].

$$\Delta T = -D \, dc_A / dx$$

   D = Drug diffusion coefficient (assumed constant); C_A= Drug concentration.

   For matrix system (drug uniformly dispersed throughout the matrix), unsteady state drug diffusion in a one dimensional slap- shaped matrix may be described using Fick's second law of diffusion.

   Drug diffusion coefficient is assumed to be constant. Other assumptions are sink condition and a thin planar geometry where the release through the edges is neglected. Drug diffusion coefficient is a function of drug concentration except in very dilute solutions. Diffusivities of encapsulated molecules depend on the degree of swelling and cross linking density of the gels for hydrogel devices. Diffusion coefficient used to describe drug release is sensitive to environmental changes or degradation of the polymer network and varies over the time scale of release [2, 7].

   a. **Reservoir Systems:** It consists of a polymeric membrane surrounding a core containing the drug. In matrix devices, the drug is dispersed throughout the three-dimensional structure of the hydrogel. Drug release from each type of system occurs by diffusion through the macromolecular mesh or through the water filled pores. Fick's law of diffusion is commonly used in modeling diffusion controlled release systems. For a reservoir system where the drug depot is surrounded by a polymeric hydrogel membrane, Fick's first law of diffusion can be used to describe drug release through the membrane: For the case of a steady-state diffusion process, i.e. constant molar flux, and constant diffusion coefficient, following expression:

$$J_i = K \, Dip \, \Delta C_i / \delta$$

   Where, δ is the thickness of the hydrogel and K is the partition coefficient, defined as the ratio of drug concentration in the gel per drug concentration in solution. To maintain a constant release rate or flux of drug from the reservoir, the concentration difference must remain constant. This can be achieved by designing a device with excess solid drug in the core. Under these conditions, the internal solution in the core will remain saturated. This type of device is an extremely useful device, allows for time-independent or zero-order release [2, 7].

   b. **For a Matrix System:** Where the drug is uniformly dispersed throughout the matrix, unsteady-state drug diffusion in a one-dimensional slap-shaped matrix can be described by the Fick's second law: This form of the equation is for one-dimensional

transport with non-moving boundaries and can be evaluated for the case of constant diffusion coefficients and concentration-dependent diffusion coefficients. For the case of concentration independent diffusion coefficients, equation can be analyzed by application of the appropriate boundary conditions [2, 7]. Schematic representation of diffusional controlled reservoir and matrix devices shown in **fig. 9**.

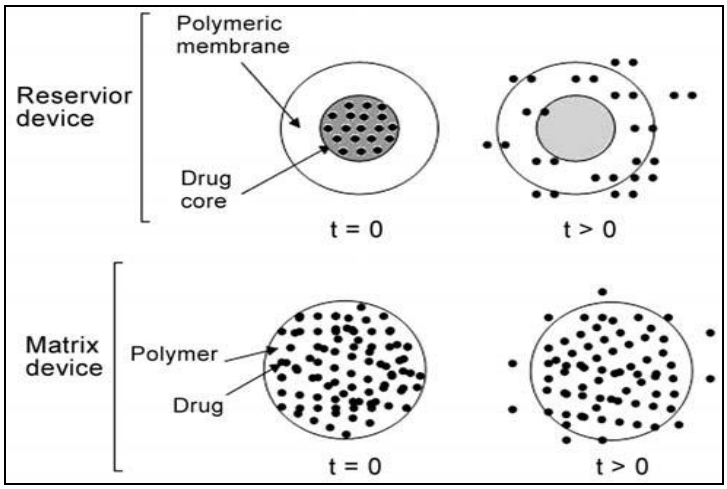

FIG. 9: SCHEMATIC REPRESENTATION OF DIFFUSIONAL CONTROLLED RESERVOIR AND MATRIX DEVICES

2. **Swelling Controlled:** It occurs when diffusion of drug is faster than hydrogel swelling. In this condition the modeling of drug involves moving boundary, where molecules are released at the interface of the rubbery and glassy phases of swollen hydrogels. Transition occurs from a glassy state where entrapped molecules remain immobile to a rubbery state where molecules rapidly diffuse. Release of small molecule drugs from HPMC hydrogel tablets are based on this mechanism. For example, Methocel matrices (a combination of methylcellulose and HPMC) from Dow chemical company prepare swelling controlled drug delivery formulations. Drug diffusion time and polymer chain relaxation time are two key parameters determining drug delivery from polymeric devices. In diffusion controlled delivery systems, the time scale of drug diffusion,

$$T = \delta(t^2)/D$$

δt (where and is the time dependent thickness of the swollen phase) is the rate limiting step while in swelling- controlled delivery systems the time scale for polymer relaxation (λ) is the rate limiting step.

In diffusion- controlled delivery system, Fickian diffusion dominates the molecule release process while in swelling- controlled delivery systems, the rate of molecule release depend on the swelling rate of polymer networks. Equation showing relationship between drug diffusion and polymer relaxation are

$$Mt/M\infty = k_1 t^m + k_2 t^{2m}$$

The two terms on the right side represent the diffusion and polymer relaxation contribution to the release profile respectively. Korsmeyer and Peppas introduced a dimensionless swelling interface number Sw, to correlate the moving boundary phenomena to hydrogel swelling

$$S_w = \delta(t)/D$$

V = Velocity of the hydrogel swelling front; D = Drug diffusion coefficient in the swollen phase

3. **Chemically Controlled:** It characterizes molecule release based on reactions occurring within a delivery matrix. Most commonly occurring reactions are-

   i. Cleavage of polymer chains via hydrolytic or enzymatic degradation.

   ii. Reversible or irreversible reactions occurring between the polymer network and releasable drug. It can be categorized on the basis of reactions occurring during drug release

a. **Purely Kinetic-Controlled Release:** Polymer degradation (bond cleavage) is the rate determining step while diffusion contributes almost negligible to the drug release. It is of two types

   i. Pendant chain (prodrugs)

   ii. Surface eroding systems

In pendent chain systems, drugs are covalently linked to the hydrogel network device through cleavable spacers and drug release is controlled by the rate with which spacer bond cleavage occurs. In specific applications where a more targeted delivery approach is desired, it is advantageous to design enzymatically cleavable spacer bonds.

In surface eroding systems, drug release is mediated by the rate of surface erosion of the polymer matrix. In hydrophobic polymer networks, surface erosion occurs when the rate of water transport into the polymer is much slower than the rate of bond hydrolysis. Nevertheless due to the inherently high water content of hydrogels, surface erosion occurs slowly in enzymatic degradation systems where the transport of enzyme into the gel is slower than the rate of enzymatic degradation [2, 7, 17].

b. **Reaction Diffusion-Controlled Release:** Reaction (polymer degradation, protein – drug interaction) and diffusion both contribute to the drug release [2, 7, 17].

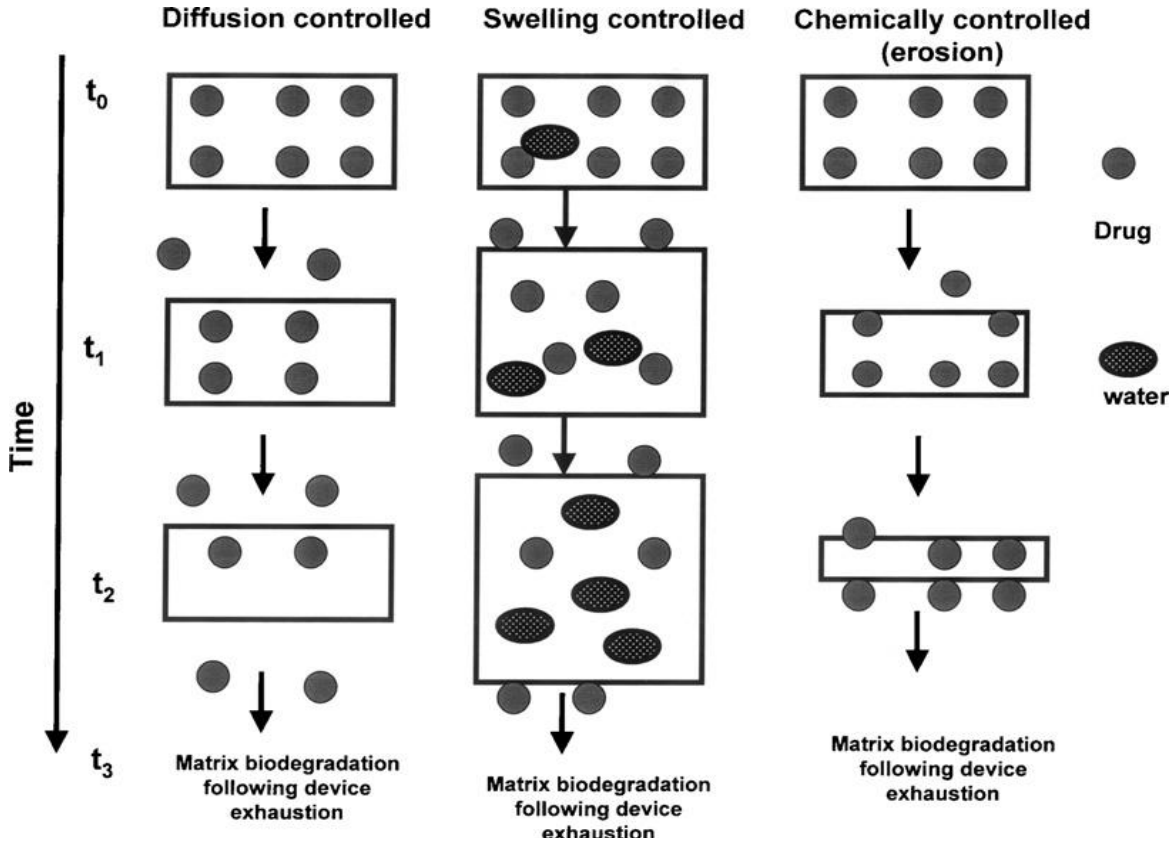

FIG. 10: A SCHEMATIC DRAWING ILLUSTRATING THE THREE MECHANISMS FOR CONTROLLED DRUG RELEASE FROM A POLYMER MATRIX

Applications of Environment-Sensitive Hydrogels in Drug Delivery:

1. **Parenteral Delivery:** One of the most obvious ways to provide sustained release medication is to place the drug in a delivery system and inject or implant the system into the body tissue. Thermo reversible gels mainly prepared from poloxamers are predominantly used. The suitability of poloxamer gel alone or with the addition of hydroxyl propyl methylcellulose (HPMC), sodium carboxymethyl cellulose (CMC) or dextran was studied for epidural administration of drugs in vitro. The compact gel depot acted as the rate-limiting step and significantly prolonged the dural permeation of drugs in comparison with control solutions. Hydrogels formed by xyloglucan were also evaluated as a sustained release vehicle for the intraperitoneal administration of mitomycin. PAA/polymethacrylic acid forms a pH-sensitive complex with PEG in situ, possessing the potential to release drug substances subcutaneously over a period of a few days [1, 2, 3, 7].

2. **Ocular Delivery:** The efficacy of ophthalmic hydrogels is mostly based on an increase of ocular residence time via Enhanced viscosity and mucoadhesive properties. Since resulted swollen hydrogel is aqueous based, it is very comfortable in the human eye. Among these polymers, in situ gels are preferred since they are conveniently dropped in the eye as a solution, where undergo transition into a gel.

Thermo sensitive, specific ion sensitive or pH-sensitive hydrogels have been examined for their potential as vehicles for ocular drugs. Poloxamers as thermo gelling polymers could be applicable for the development of effective ophthalmic drug delivery [2, 3].

3. **Peroral Drug Delivery:** The pH-sensitive hydrogels have a potential use in site-specific delivery of drugs to specific regions of the GI tract. Hydrogels made of varying proportions of PAA derivatives and cross-linked PEG allowed preparing silicone microspheres, which released prednisolone in the gastric medium or showed gastro protective property. Cross-linked dextran hydrogels with a faster swelling under high pH conditions, likewise other polysaccharides such as amide pectins, guar gum and inulin were investigated in order to develop a potential colon-specific drug delivery system [3].

4. **Rectal Delivery:** The rectal route may be used to deliver many types of drugs that are formulated as liquid, semi-solid (ointments, creams and foams) and solid dosage forms (suppositories). Conventional suppositories often cause discomfort during insertion. In addition, suppositories are unable to be sufficiently retained at a specific position in the rectum; sometimes they can migrate upwards to the colon that makes them possible for drug to undergo the first-pass effect. H.G. Choi *et al*., developed novel in situ gelling liquid suppositories with gelation temperature at 30–36°C. Poloxamer 407 and/ or poloxamer 188 were used to confer the temperature sensitive gelation property. Bioadhesive polymers were used to modulate the gel strength and the bioadhesive force. Bioavailability of acetaminophen was studied [1, 7].

5. **Vaginal Delivery:** The vagina, serves as a potential route for drug administration. Formulations based on a thermoplastic graft copolymer that undergo in situ gelation have been developed to provide the prolonged release of active ingredients such as nonoxynol-9, progestins, estrogens, peptides and proteins. J. Y. Chang *et al*., have recently reported a mucoadhesive thermo sensitive gel (combination of poloxamers and polycarbophil) which exhibited increased and prolonged antifungal activity of clotrimazole in comparison with conventional PEG-based formulation [29].

6. **Dermal and Transdermal Delivery:** Thermally reversible gel of Pluronic F127 was evaluated as vehicle for the percutaneous administration of indomethacin. *In-vivo* studies suggest that 20% w/w aqueous gel may be of practical use as a base for topical administration of the drug. Poloxamer 407 gel was found suitable for transdermal delivery of insulin. The combination of chemical enhancers and iontophoresis resulted in synergistic enhancement of insulin permeation [17].

7. **Nasal Delivery:** Nasal formulations of AEA with chlorpheniramine maleate and tetrahydrozoline hydrochloride were investigated. The findings suggest that liquid AEA formulations facilitate the instillation into the nose and the hydrogel formed on the mucous membrane provide controlled drug release [1, 2, 3, 7].

8. **Hydrogels in release of DNA:** Recently we have reported the encapsulation of deoxyribonucleic acid (DNA) into PVA hydrogels, obtained by a technique of repeated freezing and thawing. The obtained cryogels were chemically and physically characterized, and show a good mechanical resistance and a white and opaque appearance due to a heterogeneous porous structure. Furthermore, the encapsulated DNA molecules can be compacted or extended in the PVA matrix by tailoring the crystallinity degree of the PVA network. A. J. M. Valente *et al.,* developed release of DNA from cryogel PVA-DNA membranes. Poly (vinyl alcohol) (PVA) hydrogels have been used for numerous biomedical and pharmaceutical applications.

   In this communication, the effect of different factors, such as type of electrolyte, ionic strength, temperature (ranging from 20 to 40°C) and cationic surfactants on the distribution coefficients (α) and release rate constants (kR) of deoxyribonucleic acid (DNA) from PVA-DNA blend gel matrices (of a sheet shape), will be presented and discussed. The release kinetic constant and the distribution coefficient of DNA are quite sensitive to the

surrounding matrix media (e.g., kR ranges from $1.5 \cdot 10^{-8}$ to $4.7 \cdot 10^{-7}$ s^{-1}). The analysis of the temperature dependence on kR shows that the activation energy for the DNA desorption to an aqueous solution is equal to 21.2kJ/mol. These results constitute a step forward towards the design of controlled DNA release PVA-based devices [19].

Ki Woo Chun *et al*., developed Controlled release of plasmid DNA from photo-cross-linked pluronic hydrogels. Chemically cross-linked hydrogels composed of PluronicTM, water-soluble tri-blockcopolymers of poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide), were synthesized by a photo-polymerization method to achieve controlled DNA release. Pluronic F127 was di-acrylated to form a macromer and cross-linked to form a hydrogel structure in the presence and absence of vinyl group-modified hyaluronic acid (HA). UV irradiation time and the presence of the vinyl group-modified HA affected the mechanical property of Pluronic hydrogels to a great extent.

Swelling ratio, degradation, and rheological behaviors of Pluronic hydrogels were investigated. When plasmid DNA was loaded in the hydrogels for sustained delivery, various release profiles were attained by varying UV irradiation time and modified HA amounts. Entrapped DNA was gradually damaged with increasing the UV exposure time as evidenced by decreasing the transfection efficiency. The DNA fractions released from the HA/ Pluronic hydrogels, however, exhibited considerable transfection efficiencies commensurate with the UV exposure time, suggesting that they were not chemically degraded during the release period and substantially maintained functional gene expression activities despite the UV irradiation [18].

CONCLUSION: Stimuli-sensitive hydrogels have enormous potential in various applications. Some environmental variables, such as low pH and elevated temperatures, are found in the body. For this reason, either pH-sensitive and or temperature sensitive hydrogels can be used for site-specific controlled drug delivery. Hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as biosensors as well as drug delivery systems. Light-sensitive, pressure-responsive and electro-sensitive hydrogels also have potential to be used in drug delivery and bioseparation. Combining the functions of bio-molecules, such as enzymes, with pH or temperature-sensitive polymers can also lead to the construction of biomolecule-sensitive systems. Even though most biomolecule sensitive hydrogels still require further research, they are likely to become quite important biomaterials in the near future. Some of the studies described in this review will surely lead, not only to a better understanding of the structures and functions of biomolecule and environment sensitive hydrogels, but also to promising strategies for the development of novel stimuli-sensitive hydrogels.

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