National Journal of Pharmaceutical Sciences

E-ISSN: 2788-9270
P-ISSN: 2788-9262
www.pharmajournal.net
NJPS 2022; 2(2): 54-62
Received: 17-05-2022
Accepted: 15-06-2022

Kristi Vaddoriya
Sigma Institute of Pharmacy, Bakrol, Ajwa-Nimeta Road, Vadodara, Gujarat, India

Jigar Vyas
Sigma Institute of Pharmacy, Bakrol, Ajwa-Nimeta Road, Vadodara, Gujarat, India

Umesh Upadhyay
Sigma Institute of Pharmacy, Bakrol, Ajwa-Nimeta Road, Vadodara, Gujarat, India

Corresponding Author:
Kristi Vaddoriya
Sigma Institute of Pharmacy, Bakrol, Ajwa-Nimeta Road, Vadodara, Gujarat, India

Thermo-sensitive hydrogel as a carrier for topical drug delivery: A concise review

Kristi Vaddoriya, Jigar Vyas and Umesh Upadhyay

Abstract
The main aim of this article is to give an overview of the selectivity of thermo-responsive hydrogels as a carrier for topical medication administration. Hydrogels can be created by physically or chemically cross-linking hydrophilic polymers, both natural and manufactured. The hydrogels can, however, go back to their original condition following a response as quickly as the trigger is removed because these alterations are reversible. Topical gel is a safe and effective therapy option for the management of skin-related disorders, according to clinical evidence, particularly when used for local action to prevent the adverse effects of other traditional dosage forms. Gels, cream, ointment, and paste are he avoids the adverse effects of other dosage forms. The aim of this review is to inform student about the importance of stimuli responsive hydrogels in system of drug delivery, also their mechanical action. Hydrogels are currently used in the production of contact lenses, hygiene items, tissue engineering, pharmaceutical delivery systems, and dressings- Application, properties, limitation and improvements of it. The main object of these review article is different types of hydrogels in specially stimuli sensitive hydrogel like-chemical, biological, physical stimuli sensitive hydrogels. It also include figure of different types hydrogels.

Keywords: Hydrogel, topical formulation, stimuli sensitive hydrogels, thermo-sensitive gel, ion-sensitive.

1. Introduction
Topical preparations are made in a vehicle that may be adjusted to a specific body part or kind of skin problem. The product may be designed to moisturise or to enhance the administration of an active chemical, often a drug, into or through the body. Semisolid preparation definitions, such as ointments, lotions, creams, gels, and so on, vary and are sometimes imprecise. Most topical medicines, particularly those with emulsion formulations, have the potential for contamination by diverse bacteria based on rheological behaviour, water and volatiles, content, and temperature behaviour. As a result, antimicrobial preservatives are employed to prevent bacteria, fungus, and mould from growing [1].
In contrast to a capsule that is ingested or medicines placed directly into a vein, a topical formulation is medicine that is applied directly to the skin. Wet formulations, granules, shaking creams, lotions, pastes, hydrocarbons, ointments, gels, and adhesive bandages are all types of topical applications. Topical formulations are applied to the body directly.

1.1. Advantages of topical formulation
- When necessary, a higher dose of medicine is administered.
- Compared to drugs administered systemically, there are less adverse effects and less damage to other organs.

1.2. Disadvantages of topical formulation
- The application process may take some time.
- The routine can occasionally be challenging, especially if multiple different formulations are required.
- Additionally, the applications could be unclean or unpleasant.

2. Gel as a carrier for topical preparation:
Gel contain certain semisolid materials depends on physiological properties and molecular composition, The word “GEL” was introduce in 1800s, Topical gels are generally produced with polymers such as carbomers, which give the goods a clear, attractive, glittering look and are readily rinsed off the skin with the use of water.

Bases with a high concentration of oleaginous ingredients provide emollient characteristics to dry as well as irritated skin. Bases containing non-volatile oleaginous chemicals, in particular, can form barrier on the skin, preventing moisture from the atmosphere. As a result, moisture collects between the skin and the ointment layer. Some gel systems are as transparent as water, whereas others are murky because the constituents not entirely dispersed, or they form aggregates that scatter light [3]. Gels in Pharmaceuticals are Semisolid dosage form usually containing of solutions or dispersion of one or more medicaments in suitable hydrophilic bases and hydrophobic bases. Generally Suitable gelling agents are used for the preparation of gels. Preservatives, Stabilizers and Antioxidants may be added to the gels. Gels used to treat large open wounds and severely injured skin and are must sterile. Gels are three-dimensional, semi-solid polymeric matrix systems. This function similarly to solid systems; yet, they include a larger proportion of liquid components than solid dispersions. Novel drug delivery methods have shown to be particularly effective in delivering therapeutic compounds [2].

The word ‘‘gel’’ is derived from ‘‘with site-specific effects in recent years. Furthermore, these technologies allow for controlled medication release while reducing unwanted side effects. Smart gels respond to biological stimuli and environmental stimuli like temperature, chemical, enzymes, electrical, antigens, and so on can be created [4].

According to the United States pharmacopoeia, gels are semisolid formulation composed of either suspensions of large organic molecules or inorganic particles passed by a liquid. A two-phase system has a gel mass that is made up of a network of microscopic different molecule. In medical applications, water and hydro alcoholic solutions are the most commonly used. Many polymeric gels are reversible between gel and solid phases, with the fluid phase containing the dissolved/dispersed macromolecule containing the dispersed or dissolved macromolecule. Certain polymer gels, are irreversible because of their polymeric chains are covalently bonded with each other [3]. Internal network structure can form by chemical / physical linkages, also crystallites. Water, oil, and air are all examples of fluids that can be employed as an extender. A typical example of a hydrogel is edible jelly, which has the density of water [4].

2.1. Types of gel

1. Hydrogels
2. Organogels
3. Controlled release gel
4. Extended release gel
5. Hydrophilic gel
6. Amphiphilic gel
7. Non aqueous gel
8. Bio adhesive gel
9. Thermo sensitive hydrogels
10. Xerogels

Organogel: Organogel contains both solid & liquid phase. An organogel is a thermo reversible, solid material, non-crystalline, non-glassy. Organogels have various uses in art conservation, food, pharmaceutical and cosmetics [5].

Extended Release Gel: It contain of an hydrophilic complex that compressed and produce a controlled-release matrix. It is a controlled release technology. Interactions between matrix components generate erosion the presence of water, but the inner core remains dry. Erosion allows the medication to "back-diffuse" out of the gel-matrix at a regulated rate and most of the drug is freed. Characteristics of the gel matrix are the primary factor determining the rate of release [6].

Xerogels: Dried gels are xerogels. Xerogels typically have a high porosity, a large surface area, and very tiny pores. The solvent is removed under supercritical conditions, the network highly porous, low density substance called an aerogel is formed. Xerogels often have increased surface area & porosity, at very tiny pore diameters. Various metal, ethyl alcohol, water and are required in the sol-gel process for the synthesis of xerogels [7].

Non-Aqueous Gel: non-aqueous gel demonstrated rheological profiles. Ethylcellulose was effectively combined with propylene glycol dicaprylate/dicaprate to generate a non-aqueous gel. Rheological and mechanical characteristics rose significantly as polymer concentrations &polymeric chain length increased. There were strong linear relationships between mechanical and rheological characteristics [8].

Hydrophilic Gels: The interior polymer phase of hydrophilic gels creates a three-dimensional structure that retains the liquid vehicle as the outer phases. Foresees between molecules connect the solvent molecule to a polymer net that decreasing mobility and resulting in a more viscous, structured solution.

Amphiphilic Gels: Amphiphilic gels showed thermo-reversibility. These gels are formed by combining a solid gelator and liquid phase, and heating this phase at 60°C to form isotropic solution, then cooling the solution to form an opaque semisolid at room temperature. The gelation viscosity and temperature and gelator concentration increased, that show a stronger network [9].

3. Hydrogels: as a topical carrier:

Hydrogels are 3D-cross-linked networks like structure. Under even force, the absorbed solution cannot be withdrawn from swelling hydrogels [10]. Hydrogels can absorb a large amount of water in the spaces between them [11]. Presence of hydrophilic groups on the polymer chains, like -OH, -NH2, -COOH, as well as capillary action and osmotic pressure, is credited to hydrogels' substantial water absorption [12]. Because of the cross-linking between the hydrogels, resist polymer chains, disintegration in the media [13]. Hydrogel can be chemical or physical, and it protects hydrogels from dissolving despite the consumption of large volumes of liquid fluids [14].

3.1. History of Hydrogels

Lee first used the term "hydrogel" in 1894 to describe the colloidal gels made from inorganic salts. These gels are diametrically opposite to the materials that are now known as hydrogels. Danno created poly vinyl alcohol hydrogels later in 1958 by gamma irradiating an aqueous solution and cross-linking them. PHEMA demonstrated the characteristics of current hydrogels, such as cross-linked networks that may swell without dissolving and preserve their structure when exposed to excess water. Hydrogels are associated with several historical eras [11].

I) First generation capable of swell some specific stimuli like temperature and biological molecules etc. [11].
II) Second generation are cross-linked hydrogels with good mechanical strength and high swelling [11].
III) Third generation stereo complexes [11].

Lim and Sun investigated the use of calcium alginate to make microcapsules for effective cell encapsulation in 1980 [11]. Particularly, now a days the science of tissue engineering has given a lot of attention to hydrogels as regenerative and reparative matrix for organs and tissues [10].

3.2. Application of hydrogels

i. Biomedical applications [12].
ii. Biotechnological application [12].
iii. Pharmaceutical applications [12].
iv. Separation technology [12].
v. Electro conductive hydrogels & biosensors [12].
vi. Agriculture industry [12].
vii. Food industry [12].
viii. Cosmetic company [12].

3.3. Properties of Hydrogels

- Biocompatible synthetic polymers and Natural polymers have been combined to form hydrogels with improved characteristics [10].
- Natural polymers are non-toxic, biocompatible, biodegradable, and very inexpensive. In contrast, natural hydrogels have small mechanical strength [10].
- Biocompatible hydrogels, offer considerable mechanical strength but are costly & non-biodegradable [10].
- The holes and sizes of the pores in the hydrogel structure are crucial in influencing the hydrogel's ability to release medicines in physiological fluids internally and externally [15].
- Porosity, a crucial property of hydrogels, modified by altering their water attraction & cross-linking [15].

3.4. Classification of hydrogels

Hydrogels depends on method of preparation, swelling behavior and rate of biodegradation, sources and physical properties. The crosslinking process in physical gels is physical in nature. Physical mechanisms such as polymer chain complexion, chain aggregation, hydrophobic association, and hydrogen bonding are commonly used to accomplish this. A chemical technique, on the other hand, is used to generate a chemical hydrogel [12].

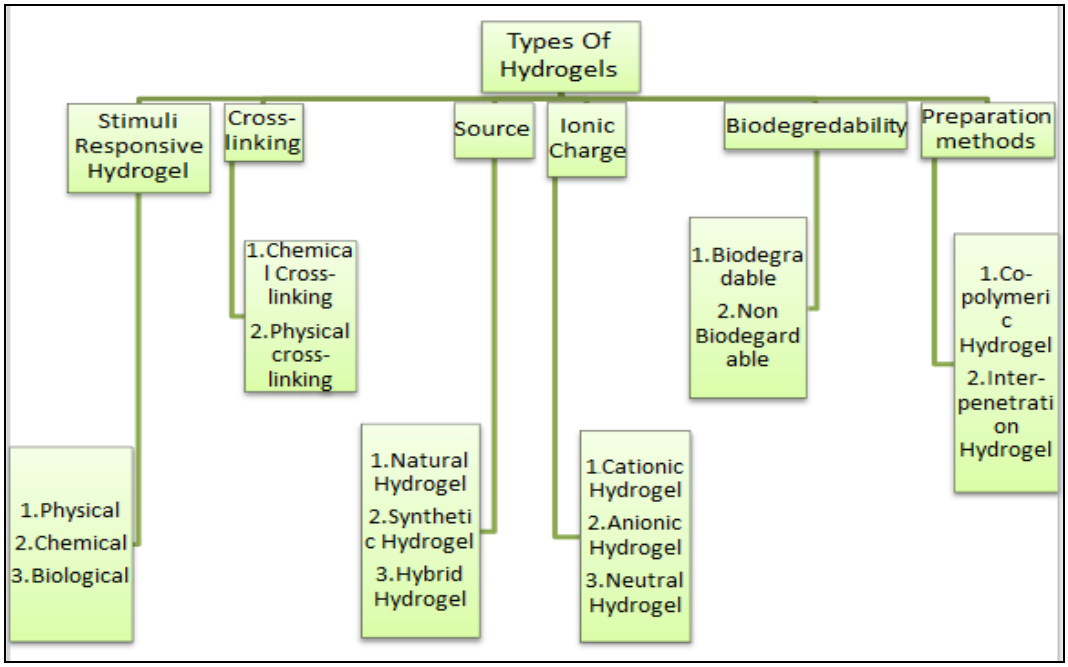


Fig 1: Types of hydrogel

4. Stimuli sensitive/responsive hydrogels:

A topical formulation is a type of drug that is administered topically rather than being eaten as a capsule or injected into a vein. Shaking lotions, Powders, pastes, creams, Wet preparations, gels, ointments, and hydrocarbons are all examples of topical treatments. There are generally 3 type of hydrogel.

i. physical stimuli sensitive
ii. chemical stimuli sensitive
iii. Biological stimuli sensitive

Except for temperature, this can be an external stimulus, biological stimuli and chemical stimuli fall into the first group, whereas physical stimuli go into the second [10]. Light, magnetic fields, electric fields, pressure, temperature, and the strength of different energy sources are examples of physical stimuli that affect molecular interactions [12].

4.1 Types of stimuli sensitive/responsive hydrogels

1. Physical stimuli hydrogel:

- Temperature
- Light
- Ultrasound irradiation
- Magnetic field
- Pressure

2. Chemical stimuli hydrogel:

- PH

- CO_2
- Ionic strength
- Redox
- Glucose

3. Biological stimuli hydrogel:

- Enzyme
- Antigen
- DNA

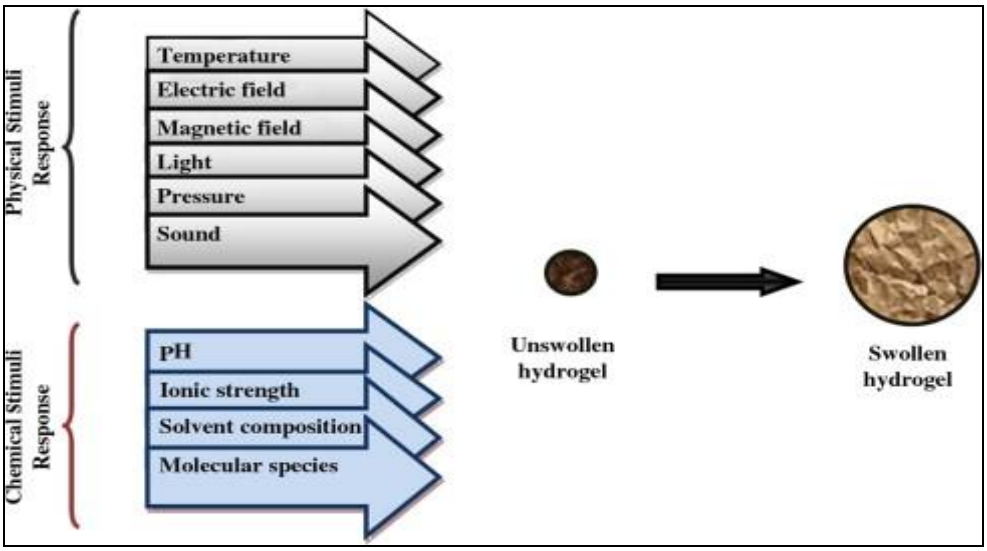


Fig 2: Types of stimuli sensitive hydrogels.

4.1.1. Physical stimuli

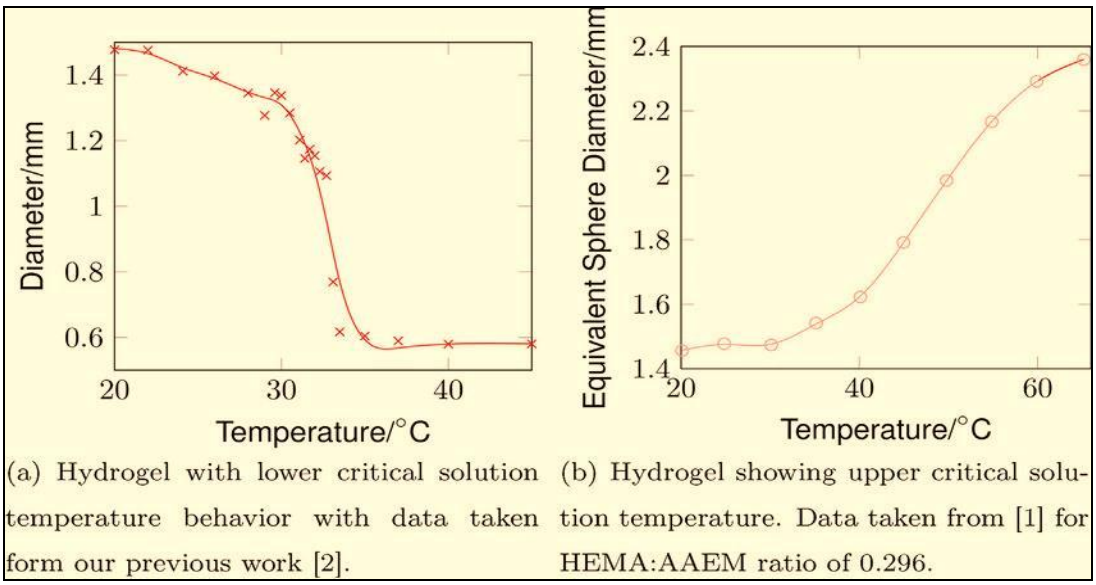
4.1.1.1. Temperature sensitive hydrogels

Temperature-sensitive hydrogels are most likely the most extensively researched family of environmentally sensitive polymer materials in drug delivery research. Poly N-isopropyl acrylamide is arguably the most widely used temperature sensitive polymer [16].

Properties of temperature-sensitive hydrogels

Most polymers become more water-soluble as temperature rises. Polymers containing LCST, on the other hand, lose water solubility as temperature rises. Inverse temperature dependency is the name given to this sort of swelling behaviour. Other hydrophobic polymers can be used in lieu of the hydrophobic PPO block.

The use of temperature-sensitive crosslinking agents expands the possibilities for developing temperature sensitive hydrogels [16].



(a) Hydrogel with lower critical solution temperature behavior with data taken form our previous work [2].

(b) Hydrogel showing upper critical solution temperature. Data taken from [1] for HEMA:AAEM ratio of 0.296.

Fig 3: Temperature Sensitive Hydrogels

Applications of temperature sensitive hydrogels

- Negatively thermo sensitive drug [16].
- Positively thermo sensitive drug [16].
- Thermo reversible gels [16].

Limitations and improvements

The monomers and cross-linkers utilised in the hydrogel synthesis are not known to be biocompatible, which means they might be carcinogenic, poisonous, or teratogenicity. The finding that acrylamide-based polymers stimulate platelets when they come into contact with blood [16].

4.1.1.2. Light-sensitive hydrogels

Light-responsive systems having the potential to function as

true biomimetic sensors. Photo-induced self-healing polymers have the potential to mirror biological systems in which damage causes a self-healing response. "gated" membranes, which regulate the movement of ions are another example of light sensitive systems [17].

Mechanism

The hydrogel may transform reversibly from its flowable state to its non-flowable form when exposed to light [10].

4.1.1.3. Pressure Sensitive Hydrogels

Several techniques for developing hydrogels with relatively high mechanical strength and high water content have been documented, including nanocomposite gel, topological gel, interpenetrating polymer networks [18]. NC gels are also highly stretchable and possess other favourable physical properties such as excellent optical transparency [19].

Mechanism

Under increasing pressure, swelling occurs. This is due to pressure increasing the lower critical solution temperature of hydrogels. The lower critical temperatures at which negative thermo-responsive hydrogels expand [9].

4.1.1.4. Ultrasound irradiation

Cellulose is gaining popularity in medicine as biocompatible polymer materials. They have exceptional qualities that are advantageous for applications, particularly in the form of hydrogels. Water retention is greater in cellulose and chitin hydrogels due to their composition. During the investigation for determining viscoelastic characteristics, it was discovered that US irradiation softened the cellulose hydrogel matrix. The hydrogels reverted to their normal viscoelastic properties once the US was stopped. This hydrogel weakening under US exposure will be useful in applications such as US medication delivery [20].

Mechanism

Ionic cross-links in the hydrogels are momentarily disrupted by ultrasound, the medication is release, but in this condition the cross-linkage is restored when the ultrasound waves are switched off. This facilitates drug release on demand [22, 23].

4.1.2. Chemical stimuli

4.1.2.1. PH Sensitive Hydrogels

Ph sensitive hydrogels require two elements,

(i). Polymer contain a physical code or chemical code that aid to regain the original form at pH 5, the cross-linked polymer stabilises the hydrogel's specific permanent shape [21].

(ii). The polymer should exhibit a stimulus-controlled phase transition property

Property of pH-sensitive hydrogels

PH sensitive is attributed to ionic hydrogels with parameters like degree of polymer concentration, ionisation, hydrophilicity, pKb values, ionic charge, pKa value and swelling medium. As a result, the polymer chains' ionised negatively charged pendant groups induce repulsion, resulting in swelling. This feature of hydrogels can be used for medication administration in the colon at pH 7.4. Cationic hydrogels such as chitosan and polyacrylamide Protonation of amino/imine groups causes swelling at low pH (acidic media) [10, 16].

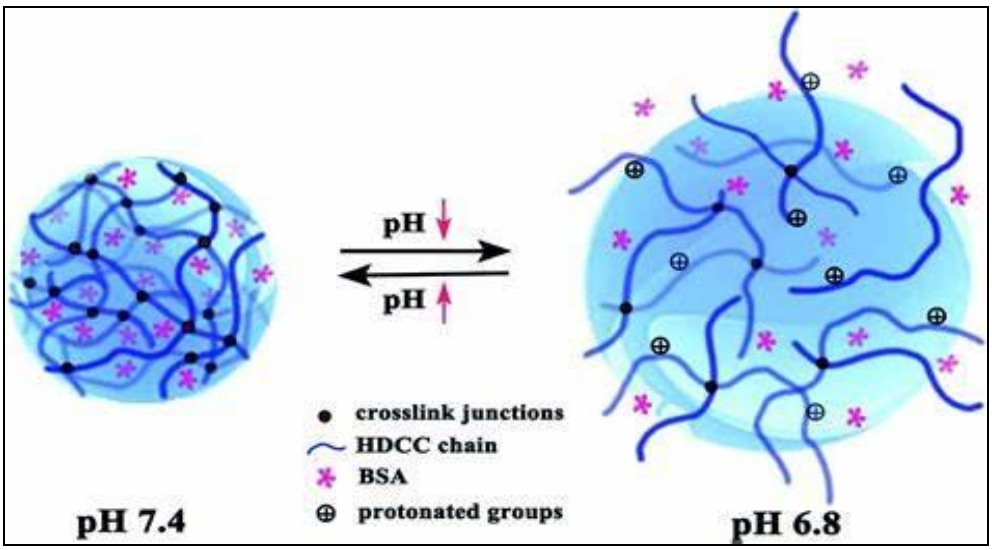


Fig 4: ph. Sensitive Hydrogels for Drug Delivery

Application of ph. sensitive hydrogels

pH sensitive hydrogels used in a variety of biosensors, including BioMEMS, which use an ethylene glycol & methacrylic acid blend. PH sensitive hydrogels intensively investigated & employed in biomedical applications, particularly in drug delivery that take advantage of pH variations throughout the GI tract [9]. Also for biomedical uses, pH sensitive hydrogels are successfully used in the engineering as microfluidic valves [24].

PH-sensitive hydrogels most commonly employed in the development of controlled release formulations for oral administration. The pH of stomach differs significantly from the neutral pH in the intestine, and this difference is great enough to cause polyelectrolyte hydrogels to exhibit pH-dependent behaviour. For colon-specific drug administration, hydrogels composed of polyanions and cross-linked with azoaromatic cross-linkers were created [16]. So, the media opens & close the micro valve based on these reactions, so controlling the flow [25, 26]. PH-sensitive hydrogels also utilised to create biosensors switches. The

production of gluconic acid reduces the pH, influencing the swelling hydrogels. Glucose oxidase, which converts glucose to gluconic acid, is a popular enzyme utilised in pH-sensitive hydrogels. These pH-dependent hydrogels are often equipped with enzymes that vary the pH of the microenvironment within the hydrogels [16].

Limitations and improvements

Non-biodegradability is one of the fundamental constraints of pH-sensitive polymers. As a result, non-biodegradable polymer hydrogels must be eliminated from the body after usage. In the human body, natural polysaccharides are not always biodegradable. Because of their structure and less flexible amino acid residues they produced from natural proteins, synthetic polypeptides were also employed in the manufacture of biodegradable hydrogels [16].

4.1.2.2. 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 [16, 17].

Mechanism

Swelling and drug release are also depends in ion concentration [28].

4.1.2.3. Glucose-sensitive Hydrogels

Cationic pH-sensitive polymers containing immobilised insulin and glucose oxidase can expand in response to blood glucose levels, pulsatilely releasing the entrapped insulin [27].

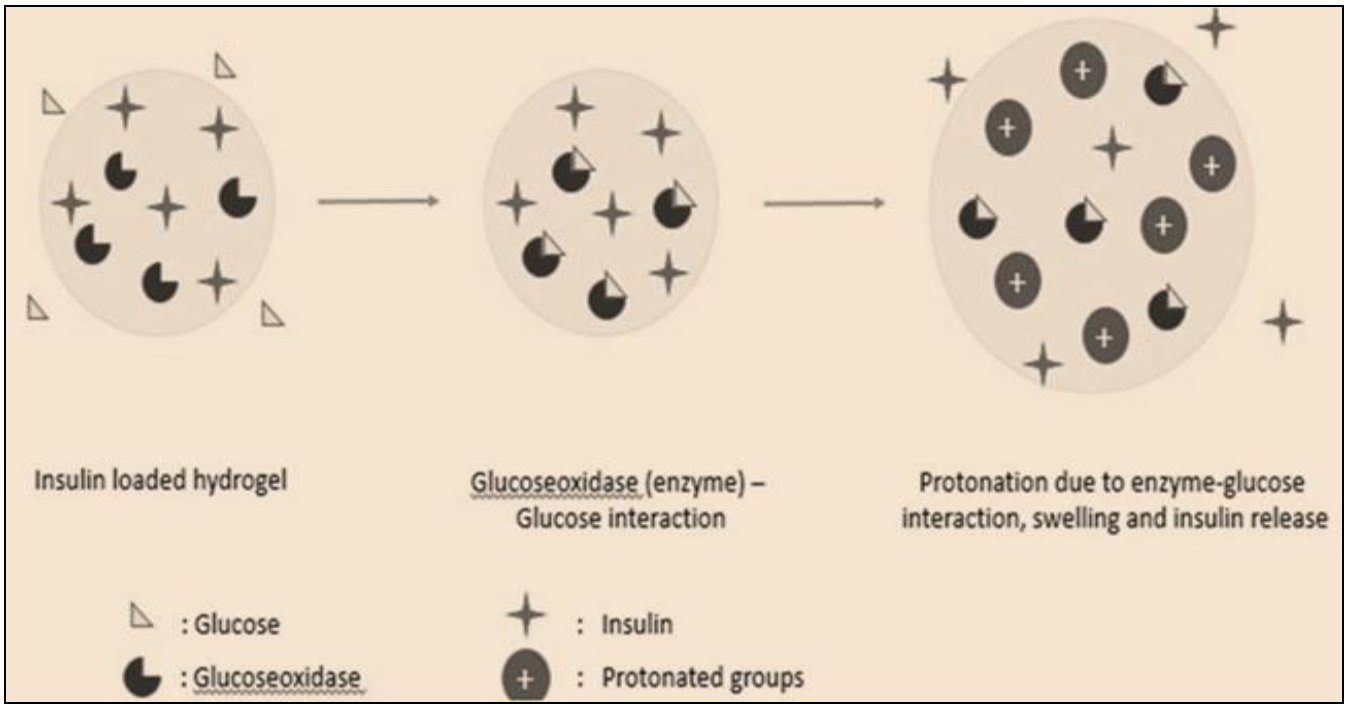


Fig 5: Glucose Sensitive Hydrogel

Mechanism

Increased glucose concentration causes hydrogels to expand. The combination generated between phenylboronic acid and glucose causes the hydrogels to expand resulting, insulin release [29].

4.1.2.4. CO_2 Sensitive Hydrogels

Mechanism

On presence of CO2, the pH of the solution changes resulting in swelling or inflammation of the hydrogel. Due to inflammation causes a pressure change [30].

4.1.2.5. Redox-sensitive Hydrogels

Redox-sensitive materials have attracted a lot of attention in now days. As three-dimensional cell-culture implants, disulfide cross-linked hydrogels can be disrupted under providing sufficient reasonable reductive conditions without affecting the effectiveness of the implanted cells [31].

Mechanism

Disulfide bonds in reduction sensitive hydrogel in the intracellular matrix's reductive environment, so releasing bioactive molecules or drugs [32].

4.1.3. Biological Stimuli

4.1.3.1. Antigen sensitive hydrogels

The structure of the hydrogel shrinks in the absence of a free antigen due to intra-chain antigen-antibody interaction in the polymer network. Hydrogels can be combined with cross-linked hydrophilic polymeric backbones that have been antibody grafted [11].

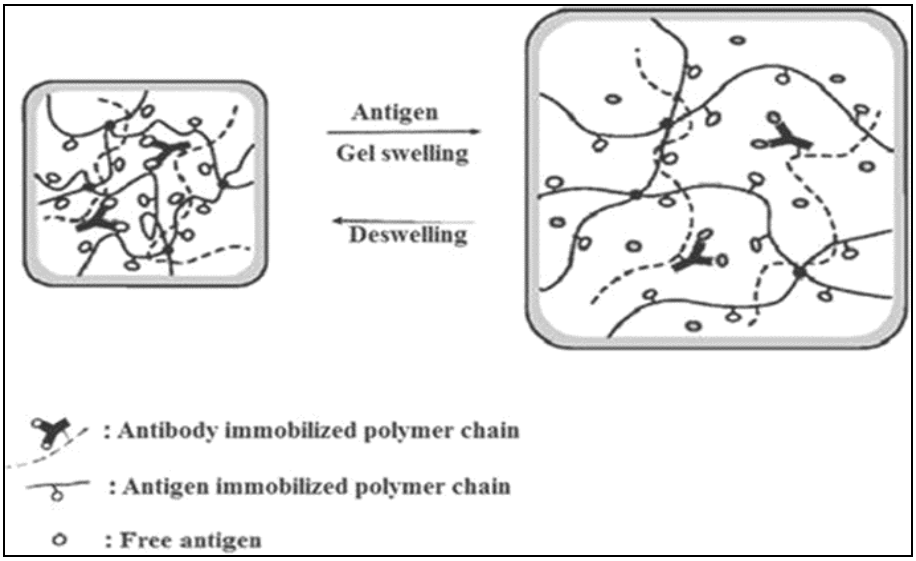


Fig 6: Antigen Stimuli Hydrogel

Mechanism

Hydrogels identify free antigens and swell, resulting in drug release [11, 33].

4.1.3.2. DNA Sensitive Hydrogels

Hydrogels are three-dimensional hydrophilic structures that range in size from Nano to macro and have several uses in health and industry. DNA hydrogels can be created by either chemically linking DNA molecules or physically entangling DNA strands [34]. Polymers are chemically bind together by covalent bonds, which give mechanical strength & environmental stability [35]. DNA hydrogels two categories,

- pure DNA hydrogels [36].
- hybrid DNA hydrogels [36].

Only DNA molecules are used to create this form of gel, and it is put together using enzymatic polymerization, Watson-Crick interactions, precise binding and enzymatic ligation of DNA motifs between its constituent DNA molecules. Pure DNA hydrogel, an alternative substance, has been developed to overcome the shortcomings of hybrid hydrogels since numerous procedures are required to modify hybrid hydrogels [37].

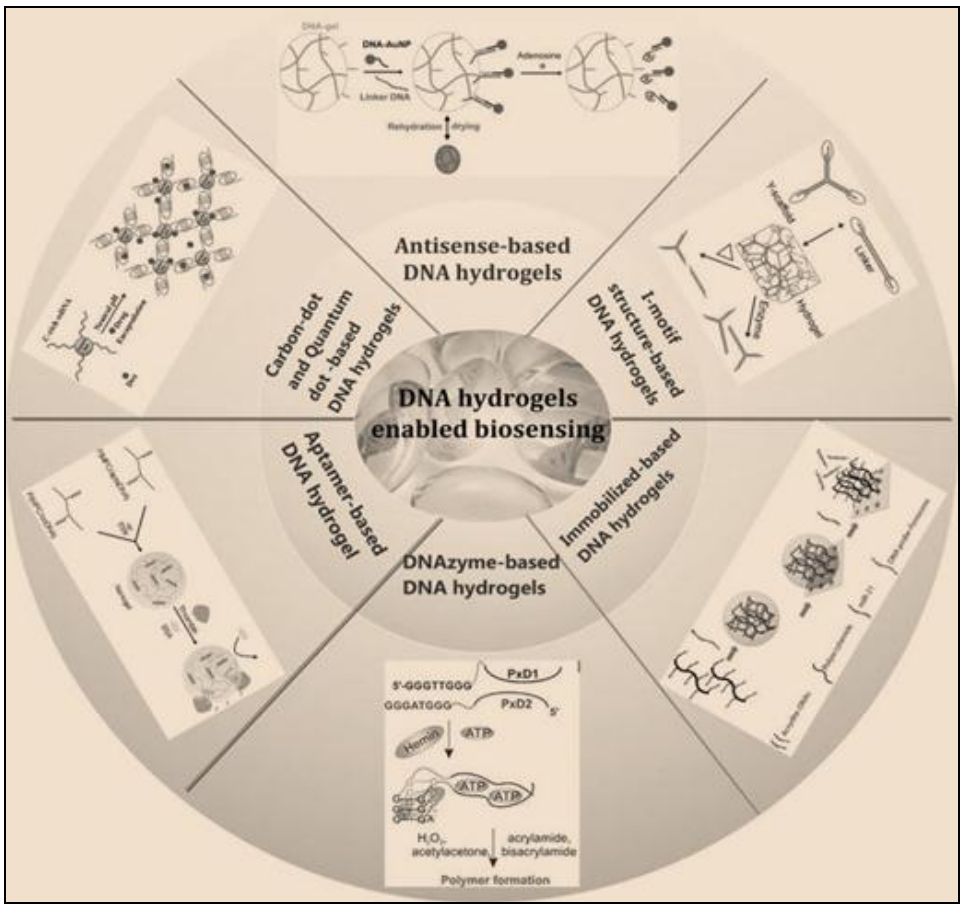


Fig 7: DNA Hydrogels Bio-sensing

Mechanism

In the presence of single stand DNA, hydrogel probes swell. [39].

4.1.3.3. Enzyme Sensitive Hydrogels

Many hydrogels may be easily micro-patterned or Nano-patterned to allow the construction of lab-on-a-chip devices, which is especially useful in bio-sensing applications. A biological recognition event is linked to a observable change in hydrogel properties in these systems. PEG is commonly used in hydrogel-based biosensor surfaces to reduce nonspecific adsorption of biomolecules. [40].

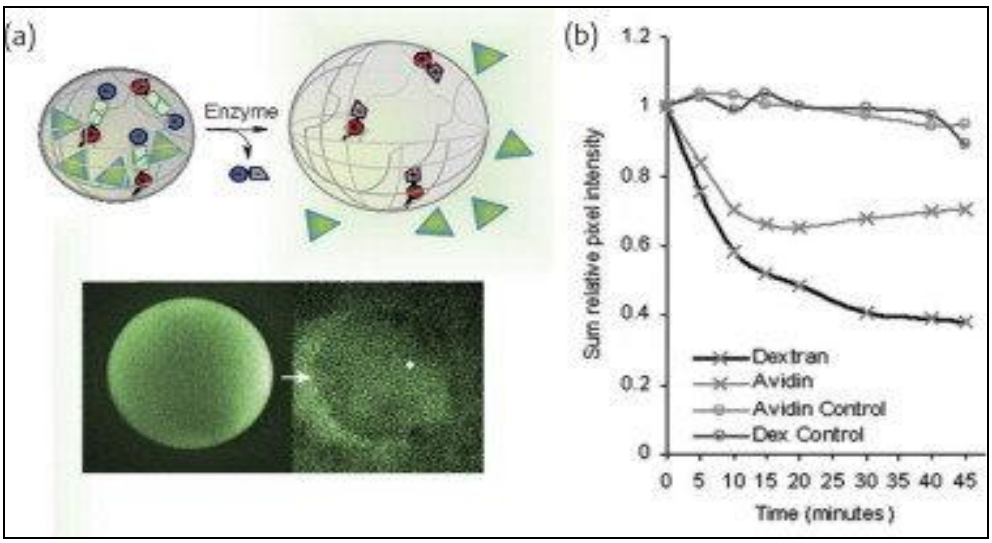


Fig 5: Enzyme Sensitive Hydrogels

Mechanism

Enzymes decomposed hydrogels as a result, drug release [41].

5: Conclusion

Hydrogels can be applied for therapeutic purpose or uses. The essential characteristics of any material to consider are biocompatibility and non-toxicity. Sensitive hydrogels have a much delayed reaction time. Among all temperature, stimuli & pH exist naturally in the human skin's interior environment. Other external stimuli like electric field & light etc. As a result, internal stimuli sensitive hydrogels with smaller sizes are used.

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