International Journal of Early Childhood Special Education (INT-JECSE)
DOI: 10.48047/INTJECSE/V14I6.369 ISSN: 1308-5581 Vol 14, Issue 06 2022

The Preparation, Mechanism, and Growth of Self-Healing Hydrogels for Biomedical Applications

ANUPRIYA ADHIKARI,
Department of Chemistry,
Graphic Era Hill University,
Dehradun, Uttarakhand,
India 248002, anupriyamahar@gmail.com

ABSTRACT –
Polymeric hydrogels have attracted a lot of attention for usage in biomedical applications due to their biocompatibility and propensity to expand in wet circumstances. Poor stimulation resistance and insufficient mechanical strength, however, pose considerable obstacles to their usage in a variety of applications. Hydrogels having the ability to self-repair after being ruptured or traumatised are a solution to this problem. Stability and durability are improved by their capacity to self-repair, reclaim lost mechanical properties, become injectable, and stretch.
The various covalent and non-covalent interactions amongst the self-healing mechanisms of these hydrogels are the primary focus of this review. Methods for studying their self-healing properties are outlined, and their uses in tissue engineering systems, drug delivery, cell encapsulation, and wound healing are discussed. Hydrogels' potential for wound healing is highlighted with a brief overview of studies on various composite materials. Incorporating composite materials into these hydrogels is a common way to boost their mechanical properties.

INTRODUCTION

Hydrogels, because to their distinctive properties, can be used in a wide variety of biological contexts. However, they have not seen widespread usage in the real world due to their subpar mechanical properties. Creating hydrogels with the ability to mend themselves is one way to go past this limitation **(Webber,2019).**
When the hydrogel is likely to be subjected to mechanical stress or damage, it is ideal that the hydrogel be able to self-heal following a breach. Reversible cross-linking of the substance is one way to make self-healing hydrogels **(He, 2020).** These cross-links can disassemble and reform in reaction to environmental changes, suggesting that the hydrogel may be able to heal itself.
Several techniques exist for making hydrogels with self-healing properties. Hydrogels can be designed to include reversible chemical links, such as imine or disulfide connections. Reversible cross-links can also be made by the use of physical interactions, such as hydrogen bonding or host-guest interactions **(He, 2020).**
Self-healing hydrogels have showed promise in a number of biological applications, including tissue engineering, drug delivery, and wound healing. Self-healing hydrogels can be used to create tissue engineering scaffolds that can withstand mechanical stress while still permitting cell growth and regeneration **(Li, 2020).** Additionally, self-healing hydrogels may be used to create drug delivery systems that can release medication in response to changes in pH or temperature in the surrounding environment **(Wang, 2020).**
The ability to respond to changes in their environment and only release medication when it's needed has piqued the interest of many researchers in the field of drug delivery. Because of their self-healing properties, which make them resilient to mechanical stress and allow them to maintain their structural integrity over time, they are useful as scaffolds in tissue engineering **(Jin, 2019).** Hydrogels that heal themselves can be used as wound dressings since they can release medicine under controlled conditions while still functioning as a barrier **(Li, 2020).**
Now that self-healing hydrogels have been discovered, sophisticated materials with improved mechanical characteristics and extended lifetimes are within reach. Reversible interactions and dynamic covalent cross-linkages have been used to create materials with self-healing properties. This

DOI: 10.48047/INTJECSE/V14I6.369 ISSN: 1308-5581 Vol 14, Issue 06 2022

has led to the development of more trustworthy, durable, and cost-effective materials **(He, 2020)**.

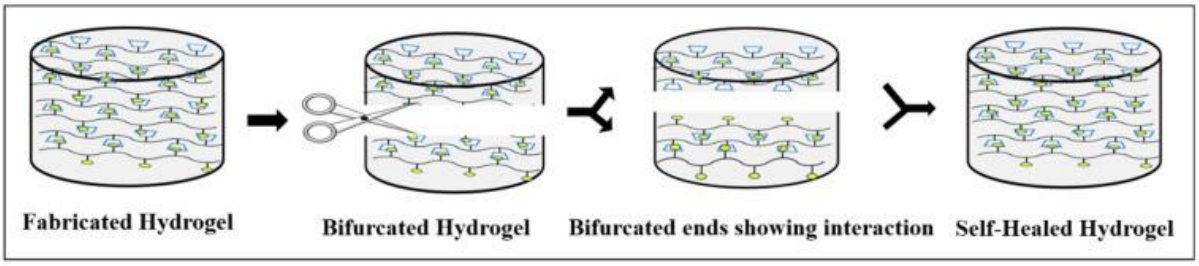

Figure 1 Demonstration of the healing process in a hydrogel.

Self-healing hydrogels, or materials that can repair themselves after being broken, are the subject of the subsequent parts of this article. Although these hydrogels offer a broad variety of potential uses, especially in biomedical research, their utilisation has been limited due to the difficulty of their manufacturing methods and the potential toxicity of the chemicals utilised **(Webber, 2019).**

This study stands out because it offers a comprehensive examination of self-healing hydrogels, including topics like the many types of self-healing processes, the role of nanotechnology in their development, and criteria for judging their efficacy. The second part of the research examines the effects of self-healing hydrogels on cell proliferation and differentiation, as well as their specialised applications in tissue engineering, drug delivery, and wound dressing.

Self-Healing Mechanism

Both covalent and non-covalent bonds are used in the production of self-healing hydrogels. The establishment of covalent bonds between polymer chains is necessary for the creation of a very stable hydrogel **(Jalalvandi, 2019).** Disulfide bonds, oxime bonds, acylhydrazone connections, and imine bonds are all examples of covalent bonding processes **(Wahid, 2018).** Hydrogen bonds, ionic contacts, host-guest interactions, and hydrophobic interactions are examples of non-covalent bonding between polymer chains that are far weaker than covalent bonding **(Jalalvandi, 2019, Jin, 2019).**

Because the connections formed by non-covalent interactions are easier to break and reestablish, hydrogels formed in this way are more flexible and self-healing. Understanding the various bonding mechanisms and their characteristics is crucial for the development of self-healing hydrogels.

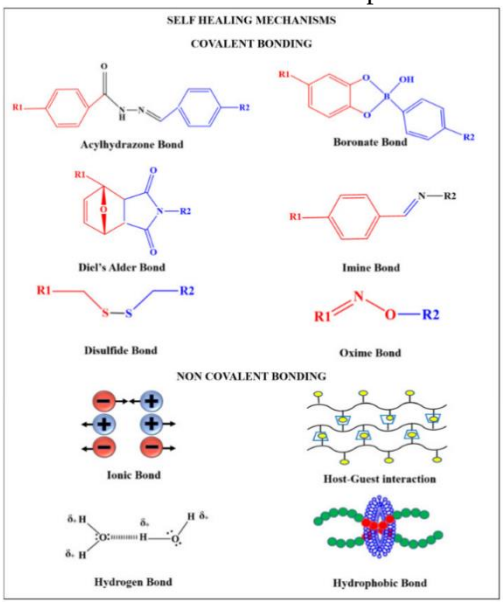

Figure 2 Bonds involved in self-healing mechanisms.

1.1. Hydrogen Bonding

Hydrogels are highly water-retentive polymeric networks in three dimensions. To create crosslinked hydrogels, polymer chains are chemically, ionically, or hydrogen-bonding linked together. Interactions between hydrogen atoms and strongly electronegative elements, such as nitrogen,

oxygen, or fluorine, result in hydrogen bonding-based crosslinking, a reversible process **(Chen, 2018).**

Applications where self-healing hydrogels might be useful include drug delivery, tissue engineering, and wound care. The bonds in hydrogels formed by hydrogen bonding contacts are more robust and the hydrogels' self-healing capacity is greater than that of those formed via ionic and covalent connections, but the hydrogels formed via hydrogen bonding contacts are less robust.

Hydrophobic water-shielding groups can be included into the hydrogel network to increase the durability of hydrogen bonding-based self-healing hydrogels **(He, 2020).** Using modified hyaluronic acid, cytosine, and guanosine, **(Webber, 2019)** showed how to create a self-healing hydrogel without the need of healing agents.

Poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate) was combined with the water-soluble galactomannan guar gum to create a conductive hydrogel. In order to hasten recovery, this hydrogel was developed to encourage wound closure and tissue reorganisation **(Webber, 2019).**

Self-healing hydrogels have also been made using the freeze-thaw method. Polyvinyl alcohol (PVA) hydrogels, for instance, have enough unbound hydroxyl groups along the PVA chain to form hydrogen bonds at the fracture site. Hydrogels with tailored mechanical characteristics and self-healing abilities may be fabricated using this method **(He, 2020).**

2.2. Ionic Bonds

Crosslinking in polymeric solutions can be stimulated by interactions between polymers having opposite charges. Self-healing is made possible by the reversible process of ionic interaction between free ions and polymers, which allows free ions to move to crosslinked or damaged portions of the polymeric chain **(Chen, 2015).**

Hydrogels capable of self-repair have been created **(Chen, 2018)** using ionic bonding and Fe3+ ions. For instance, the mechanical strength and self-healing properties of polyacrylic acid (PAA) can be improved by the formation of an ionic link between Fe3+ ions and the carboxylic groups in PAA. Even after 1000 cycles, the PAA-Fe3+ hydrogel formed retains 200% of its initial length. For usage in tissue engineering, Fe3+ can serve as a crosslinker in nanocomposite hydrogels to produce self-healing hydrogels with improved mechanical strength and other novel features **(Li, 2021).**

Ionic hydrogels have also been developed using catechol. Catechol-grafted chitosan and the electrostatic crosslinking of Fe3+ ions are used to create hydrogels with load-bearing and self-healing properties. After being subjected to a cyclic time sweep for 100 s, these hydrogels recovered their original strength. When dopamine and catechol groups were synthesised and attached to the surface of montmorillonite hydrogel, similar results were seen; after being subjected to oscillatory pressures with 100% amplitude, the molecules regained 70% of their initial storage moduli **(Li, 2021).** This is because the catechol and ferric ion pair induces a self-healing property in each other through ionic interaction.

Restoring 90% of their compressive capabilities after repair and showing time-independent healing behaviour, carboxybetaineacrylamide self-healing hydrogels containing zwitterionic material may be mended with ionic bonds **(Chen, 2018).**

Host-Guest Interactions

Supramolecular materials demonstrating host-guest interactions have garnered a lot of interest in the field of biological research because of the complementary nature of these interactions. Supramolecular hydrogel systems have been used for a variety of applications, and have included a wide variety of guest groups such as adamantane, ferrocene, azobenzene, cholic acid, and cholesterol **(Li, 2021).**

Using 6-cyclodextrin (6CD) as the host molecule and ferrocene (Fc) functionalized in the host material, Masaki et al. developed a redox-responsive hydrogel. Hydrogel's self-healing properties can be attributed to CD and Fc's mutually attractive roles as hosts and guests. Self-healing and shear-thinning properties are exhibited rapidly by a CD and Ad-grafted supramolecular hyaluronic acid hydrogel. There is an inclusion complex between adamantine (Ad) and CD. Self-healing properties are another strong suit of cyclodextrin-based hydrogels **(Webber, 2019).**

Hyaluronic acid may be methacrylated to produce hyaluronic acid-methacrylate (MeHA), which can then be crosslinked with CD-Ad to produce a hydrogel with dual crosslinking. Shear-thinning capabilities during layer-by-layer assembly makes CD-MeHA/Ad-MeHA hydrogels a promising ink for layer-by-layer hydrogel synthesis. **Kohei et al** employed a dual host-guest system using -

cyclodextrin-Adamantine and -cyclodextrin-Ferrocene complexes to create stimuli-responsive multifunctional hydrogels with self-healing and shape-memorable properties.

Self-healing behaviour in less than a minute has also been seen in inclusion complexes involving cholic acid with CD, pluronic F180 with CD, and -bromonaphthalene polymer with CD. To increase their mechanical strength and stability and make them appropriate for use in wound healing applications, cationic CD oligomers have been crosslinked with epichlorohydrin, modified with allyl glycidyl ether, and modified with glycidyl trimethylammonium chloride **(Webber, 2019).** In addition, the host-guest interaction between the hydrophobic cyclodextrin and the aromatic residues of gelatin contributes to the shear-thinning properties of a hydrogel made from cyclodextrin-modified alginate and methacrylated gelatin, which has potential in tissue engineering applications.

2.4. Hydrophobic Bonds

Chemical crosslinking techniques rely on hydrophobic interactions to produce hydrogels with self-healing properties. One such strategy is the reversible reaction of a diene and a dienophile, as in the Diels-Alder reaction **(Wang, 2019).** The monomers in self-healing hydrogels are often selected for their hydrophobic interactions with one another. The diene and dienophile in this process are the furan and maleimide functional groups, respectively. Crosslinking of PEG modified with maleimide and furan gives the hydrogels their self-healing capabilities. Hydrogels had a break elongation ratio of 1300% and repaired at a 94% efficiency in 60 seconds **(Balitaan, 2020).**

Hydrogels that repair themselves have been developed using nanotechnology and physical and chemical crosslinking processes. Nanoparticles have been used as fillers in hydrogels to increase their tensile strength, stiffness, and toughness **(Ponsubha, 2020).** Incorporating gold nanoparticles as fillers into poly (ethylene glycol)-based self-healing hydrogels, for example, significantly improved the hydrogels' mechanical properties. To improve their mechanical properties, silica nanoparticles have also been included into polyacrylamide-based self-healing hydrogels. Hydrogels that repair themselves in response to stimuli have also been made with nanoparticles. For instance, poly (N-isopropylacrylamide) hydrogels and magnetic nanoparticles were used to develop a self-healing magnetic hydrogel **(Webber, 2019).**

Self-healing hydrogels are gaining popularity, especially in the biomedical industry. Using nanoparticles, physical and chemical crosslinking processes, and improved mechanical features, self-healing hydrogels have been produced with potential drug delivery and tissue engineering applications. Research is needed to figure out how to make self-healing hydrogels on a large scale with safer materials and simpler manufacturing processes **(Webber, 2019).**

2.5. Imine Bonds

Amine-based hydrogels have showed great potential as self-repairing drug delivery systems. For instance, Schiff base formation was used to create a self-healing chitosan-PEG hydrogel for the sustained release of curcumin **(Ponsubha, 2020).** In addition to imine-based self-healing hydrogels, poly(amidoamine) dendrimers modified with aldehyde groups and polyethylene glycol have found use in brain tissue engineering. Hydrogels began self-healing after only 24 hours with a single fracture under physiological conditions **(Balitaan, 2020).**Overall, imine-based self-healing hydrogels show great potential in a number of biological applications due to their dynamic covalent bond formation, fast reaction times, and benign reaction conditions.

The prospective applications of Schiff base-based self-healing hydrogels in domains such as tissue engineering, drug delivery, wound healing, and hemostasis have generated considerable interest. The dynamic nature of imine bond production permits effective self-healing capabilities, and the use of organic materials like chitosan and alginate can guarantee both self-healing and biocompatibility. The possible medicinal applications of these hydrogels require more research **(Webber, 2019).**

2.6. Disulfide Bond

Researchers showed how to make a hydrogel that can repair itself by combining poly(ethylene glycol)-co-thioketal (PEG-TK), a disulfide-containing polymer, with dithiothreitol (DTT), a reducing reagent that can break and reestablish disulfide bonds. Hydrogel's self-healing characteristics, robust mechanical qualities, and controlled drug release were particularly impressive **(Balitaan, 2020).** Self-healing hydrogels were developed by another research team using oxidised dextran and thiolated chitosan. Self-healing and dynamic covalent crosslinking are the results of a disulfide bond between the thiol group in chitosan and the aldehyde group in dextran.

The self-healing hydrogel developed by Zhang et al. likewise makes use of cysteamine, a thiol-containing small molecule, and Poly(ethylene glycol)-b-Poly(disulfide amide) (PEG-PDS). Hydrogel has a strong self-healing ability and has slower drug release kinetics **(Chen, 2018).**

2.7. Acylhydrazone Bonds

The arylhydrazone bond is a sort of dynamic covalent binding that might be used in self-healing hydrogels for tissue engineering and wound healing. In an acidic environment, hydrazine groups can link with aldehyde or ketone groups to generate these compounds. When broken, the resulting acylhydrazone connections may nearly instantly repair themselves **(Webber, 2019).** These links can be formed by either an exchange or hydrolysis process.

There has been a lot of study into the possibility of using arylhydrazone linkages in self-healing hydrogels. One study, for instance, combined sodium alginate dialdehyde and 3,3′-dithiobis(propionohydrazide) functionalized poly(ethylene glycol) to make a self-healing hydrogel for application in tissue engineering **(Balitaan, 2020).** In a different study, researchers used chlorhexidine acetate, oxidised dextran, acid dihydrazide, and acylhydrazone links to accelerate wound healing and maintain bFGF production.

Hydrogels with self-healing capabilities have been developed using novel arylhydrazone linkages **(Li, 2020).** A macroporous hydrogel with a microporous structure can be made, for instance, by establishing azylhydrazone connections between gelatin, oxidised sodium alginate, and adipic acid dihydrazide. Polyethylene oxide was used to create a self-healing hydrogel, and the aldehyde group of tris(4-formylphenoxy) methyl ethane was used to create acylhydrazone connections. These results highlight the promise of arylhydrazone linkages in self-healing hydrogels for use in tissue engineering and wound healing **(Li, 2020).**

2.8. Diels-Alder Reaction

By introducing furan and maleimide end groups into poly(ethylene glycol) (PEG) by a reversible Diels-Alder method, a self-healing hydrogel was developed. Using a dynamic and reversible cross-linking technique based on the Diels-Alder reaction, injectable hydrogels with outstanding mechanical features and robust self-healing powers were created **(Li, 2020).** Hydrogels with stimuli-responsive drug release and self-healing characteristics have been developed using the Diels-Alder process for biomedical applications **(Chen, 2018).** These hydrogels respond to changes in temperature, pH, or light.

2.9. Boronate Bonds

Boronate ester crosslinking was employed to create self-healing hydrogels with enhanced mechanical characteristics from chitosan and PEG. Boronate ester linkages are sensitive to pH, which contributed to the hydrogel's increased mechanical strength and capacity to mend wounds. Hydrogel had promising tissue engineering and drug delivery applications due to its high cell survival rate and biocompatibility **(Chen, 2019).**

2.10. Oxime Bonds

To create an injectable hydrogel with improved mechanical and swelling properties, reversible oxime linkages were established between the aldehyde groups of oxidised dextran and the hydroxylamine-modified hyaluronic acid **(Chen, 2019).** Hydrogels prepared by oxime bonding hyaluronic acid and aldehyde-modified poly(N-isopropylacrylamide) have demonstrated the ability to swell and de-swell reversibly in response to changes in temperature and pH, making them promising candidates for controlled drug administration. Incorporating oxime bond formation in protein-polymer conjugates has also led to the development of stimuli-responsive hydrogels with potential uses in tissue engineering and drug delivery.

3. Evaluation of the Ability to Heal Itself

3.1. Standardised Evaluations of Self-Repairing Hydrogels

Self-healing properties of the hydrogel were shown by its capacity to recover its original shape after being immersed in water. In addition, when the two hydrogel samples were brought together, the dynamic bond creation allowed them to gradually blend into one another. Tiny amounts of the dye rhodamine R were employed to visually distinguish between the two components. After then, the self-healing abilities of the hydrogel were evaluated visually.

The hydrogel's resistance to stretching and splitting was measured using a simple test that involves straining it with tweezers to illustrate self-healing in action. The hydrogel's tensile strength is demonstrated here.

DOI: 10.48047/INTJECSE/V14I6.369 ISSN: 1308-5581 Vol 14, Issue 06 2022

The hydrogel's self-healing abilities were also evaluated using the scratch-and-heal technique. Scratching the hydrogel's surface and then applying a buffer solution with a pH of 7.4 is what this technique entails. After ten minutes, the hydrogel is ready to be examined using an optical microscope. These results show that the hydrogel can mend itself, opening up possibilities for use in engineering and medicine **(Li, 2020).**

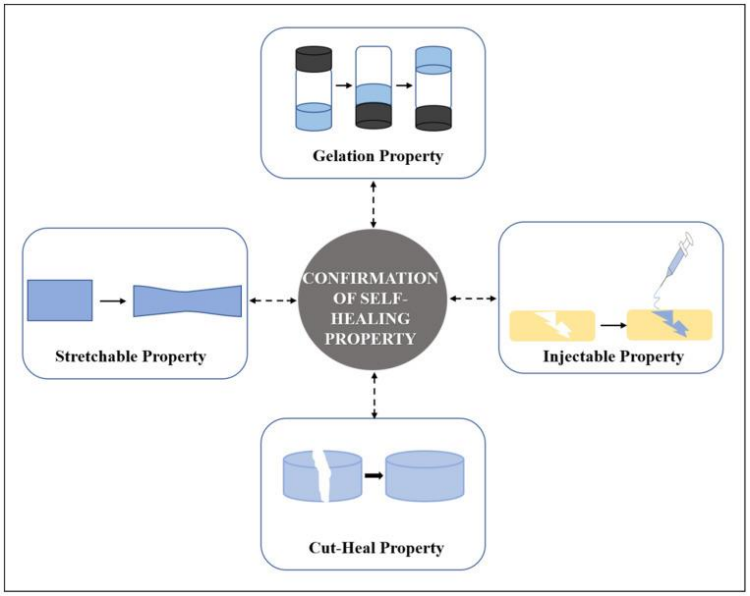

Figure 3. Tests that show a hydrogel has self-healing abilities.

3.2. Evaluation of Rheological Recovery

To analyse the hydrogel's mechanical characteristics and deformation behaviour, a continuous step strain mechanical test can be performed. Here, the material is damaged more severely, which might reveal information about its resilience and capacity to heal itself.

Important parameters discovered via rheological testing of hydrogels include storage modulus (G') and loss modulus (G"). The loss modulus reveals how much energy is lost due to viscous processes, whereas the storage modulus reveals how much elastic energy the material is capable of storing. Hydrogels' mechanical characteristics and responses to various loads may be explained by taking these into account **(Ding, 2020).**

Hydrogels' self-healing abilities may also be measured by the strain amplitude test. Hydrogel's critical point for phase transition from solid to liquid may be identified by subjecting it to a range of strain amplitudes. This provides insight into the material's structural repair and restoration capabilities **(Chen, 2019).**

A rheometer may be set up to study the hydrogelation procedure and mechanical characteristics. The material's viscoelastic properties may be evaluated by studying how it reacts to vibrations of varying frequency **(Wahid, 2018).** Dynamic oscillatory frequency sweeps and dynamic time sweep tests are two common methods used to evaluate the viscoelasticity of hydrogels and learn more about their stiffness, elasticity, and damping characteristics.

4. Uses for Hydrogels That Can Repair Themselves

4.1. Hydrogels with Enhanced Ability to Heal Wounds

4.1.1. Hydrogels that heal themselves have important applications in wound care.

Cuts and scrapes are examples of superficial skin injuries that heal quickly on their own. Natural mechanisms can still help superficial wounds heal when the epidermis and a piece of the underlying dermis are removed **(Ding, 2020).** The body's wound healing process kicks into gear under these conditions, beginning with the migration and proliferation of cells to the damage site, followed by the development of new blood vessels and the deposition of extracellular matrix components. Although it may take a few weeks, this therapy usually results in a full recovery from the wound **(Ding, 2020).**

However, the body's normal healing mechanism may not be adequate for deep wounds with a diameter greater than 1 mm. This can lead to the development of non-healing wounds since the systemic host defence mechanism is destroyed and the wound environment is exposed for a longer period of time. Additional therapies, such as debridement (the removal of dead tissue), antibiotics,

advanced wound dressings, or skin substitutes, may be required to enhance healing in some cases **(Wahid, 2018).**

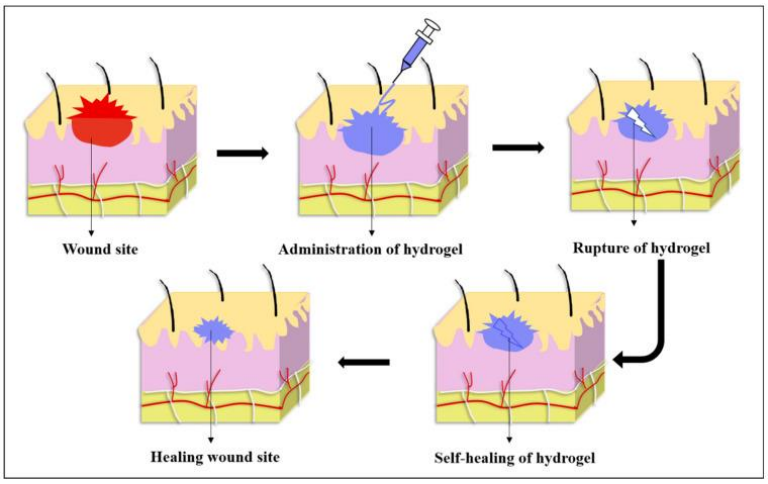

Figure 4 Wound repair using self-healing hydrogel

4.1.2. Improvements in Wound Healing Through the Use of Self-Healing Hydrogels

Self-healing hydrogels, which can speed up wound healing and closure, have been at the focus of recent advances in wound dressing materials. These hydrogels are versatile due to their adhesive, conductive, and contractile capabilities, and they can boost the biomechanical and biochemical activity of wound healing **(Wahid, 2018).**

Hydrogels designed to promote healing on their own have been created for a variety of wound types, including diabetic and chronic wounds. For instance, Qian and colleagues' self-healing hydrogel using chitosan, silk fibroin, and platelet-rich plasma showed improved wound healing in a rat model of type 2 diabetes **(Ding, 2020).**

Self-healing hydrogels for wound healing have also been developed by other researchers using materials including poly—L-lysine, oxidative hyaluronic acid, acryloyl-6-aminocaproic acid, pH-responsive multifunctional hydrogels produced from pluronic F127, and tannic acid and poly(ethylene glycol) **(Wahid, 2018).** These hydrogels have the potential to speed up wound healing and get around the drawbacks of conventional wound dressings.

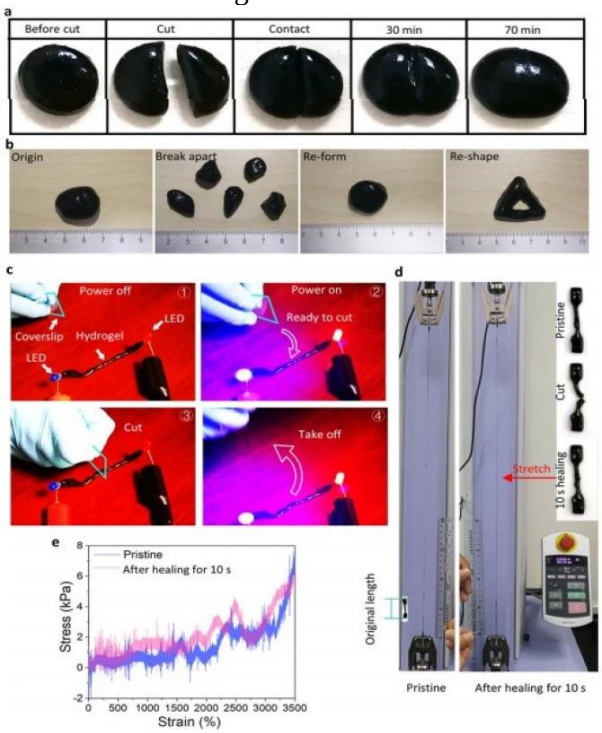

Figure 5 Methods to confirm self-healing ability of hydrogel

a) Cut heal ability within 70 min without stimuli
(b) Shape changeable capability
(c) Circuit obtained with the hydrogel that can selfheal
(d) Stretchability performed with tensile testing apparatus with pristine and self-healed hydrogel
(e) Stress-strain curves obtained from previous stretchability experiment

4.1.3. Wound Healing Hydrogels Inspired by Mussels

Dopamine and other compounds with inspiration from mussels have demonstrated promising results in biological research, especially in the field of wound healing. Using dopamine's adhesive capabilities, hydrogels with self-adhesive and dynamic cross-linking properties have been created **(Wahid, 2018).** Oxidised sodium alginate, acrylamide, chitosan, graphene oxide, hyaluronic acid, and -polylysine have all been mixed with dopamine to produce hydrogels with conductivity, various pH responsiveness, and antibacterial characteristics. These hydrogels derived from mussels are very stretchable, heal wounds quickly, and can repair themselves. In conclusion, the advantages of mussel-modified materials over conventional wound dressings have been documented **(Chen, 2019).**

4.1.4. Wound Healing Hydrogels with Nanoparticles

Because of their potent antimicrobial effects, silver nanoparticles have also seen extensive application. For instance, chitosan hydrogels doped with silver nanoparticles (AgNPs) have been found to hasten wound healing and protect against bacterial infection. Hydrogels doped with silver nanoparticles (AgNPs) in polyvinyl alcohol and gelatin showed similar antibacterial and wound healing benefits. The antibacterial and anti-inflammatory characteristics of zinc oxide nanoparticles have led to their usage in hydrogels for wound healing **(Wei, 2018).**

4.1.5. Hydrogel with Self-Repairing Bacterial Cellulose for Wound Dressing

Tissue engineering, drug administration, and wound healing are just a few of the possible uses for bacterial cellulose as a hydrogel system **(Ponsubha, 2020).** Several strategies have been investigated by researchers with the hope of improving its qualities and capabilities.

Recently, Khamrai et al. used a curcumin-loaded gelatin and an ionically modified bacterial cellulose composite to create a self-healing wound patch. This method was shown to have a positive impact on the environment and speed up the healing process of wounds by inhibiting the growth of germs **(Ponsubha, 2020).**

In a different study, a modified type of bacterial cellulose was crosslinked using imine bonds and silver nanoparticles. The ionic interactions between the components gave the final hydrogel excellent self-healing characteristics **(Balitaan, 2020).** The researchers also saw potential uses for this hydrogel in wound treatment.

A polyelectrolyte film with dynamic self-healing characteristics was built out of chitosan and negatively modified bacterial cellulose. **Wahid (2018)** suggests that this movie could help wounds heal faster since it contains medications.

Using ultraviolet (UV) irradiation to polymerize cellulose grafted with polyacrylic acid and polyvinyl alcohol resulted in the creation of a dynamic double-networked antibacterial hydrogel. Both the hydrogel's pH sensitivity and its ability to hold water were enhanced as a consequence.

Carboxymethyl cellulose, a modified type of cellulose, has been the subject of substantial research into its possible use as a wound healing agent. It shows great promise as a wound dressing material due to its amazing stretching characteristics, which allow it to grow up to 2.5 times its original size **(Balitaan, 2020).**

Polyvinyl alcohol-borax gel, reinforced with dopamine grafted with oxidised carboxymethyl cellulose and cellulose nanofibers, was used to create a composite hydrogel for wound dressings, as reported in a recent study. As a result of several covalent interactions, this hydrogel exhibits exceptional antibacterial activity, self-healing capabilities, and high mechanical qualities **(Chen, 2018).**

Furthermore, sodium alginate functionalized with an aldehyde in a Schiff base reaction is combined with carboxymethyl cellulose to create an injectable nanofiber for wound healing **(Wahid, 2018).** Mechanical and gelling characteristics of the produced nanofiber were excellent. The nanofiber's potential for wound healing was shown in a full-thickness wound model in rats, where it facilitated wound closure.

4.1.6. Incorporate 3D and 4D bioprinting to create self-healing hydrogels

There has been a lot of interest in 3D bioprinting's potential for application in wound care in recent years. Several bioinks have been developed for 3D printing scaffolds for use in tissue engineering **(Chen, 2018).** These include modified hyaluronic acid, carboxymethyl cellulose, dialdehyde dextrin, gelatin, polyethylene glycol diacrylate, N-isopropyl acrylamide, N, N-methylene bis (acrylamide), sodium alginate, and polycaprolactone.

Effective 3D printed structures have been made using the supramolecular assembly of host-guest complexes including modified hyaluronic acid and adamantane or -cyclodextrin **(Ding, 2020).** Host-guest interactions of hyaluronic acid multilayered structures were built using 3D bioprinting and cucurbit[n]urils and 1,6-diamino hexane. Methacrylate is used to enhance the mechanical properties of hydrogels by speeding up the cross-linking process.

The hydrogel was made by **Amit Kumar Sharma et al**. by combining 1:1:10 proportions of carboxymethyl cellulose, dialdehyde dextrin, and gelatin. Glutaraldehyde served as the crosslinker, and borax was used as the binding agent. 3D printing is a practical production method because of its high shear thinning and injectability.

More study is needed to increase their performance as 3D printed self-healing dressing materials in terms of self-healing and cell adhesion **(Ding, 2020).** Time is needed to create structures using 4D printing, one of the most advanced 3D printing technologies. There are a number of polymeric materials available for use in tissue engineering **(Ding, 2020).**

There has been much research on the possibility of using the self-healing polymer polycaprolactone as a scaffold in 3D bioprinting for a variety of purposes. As part of an experiment, scientists built a self-healing, form-memory 4D-printed scaffold. To create the framework, 2-ureido-4[1H]-pyrimidinone-motif polycaprolactone dimethacrylate was employed. The role of cell adhesion and proliferation in wound healing is an area that might benefit from more study **(Wei, 2018).**

4.2. Hydrogels for Drug Delivery with Self-Healing Properties

Hydrogels' resilience to damage makes them ideal for use in biological applications such medication delivery, tissue engineering, and wound healing **(Ding, 2020).**

Self-healing hydrogels have several benefits over traditional hydrogels when it comes to medication delivery. For instance, by adjusting the strength of the cross-links inside the hydrogel, they can give better regulated drug release kinetics. They can also postpone the release of drugs, reducing the need for dosing as often **(Wei, 2018).** Hydrogels have the potential to self-repair, reducing the risk of local toxicity or other unintended consequences associated with the discharge of large doses of drug **(He, 2020).**

Overall, self-healing hydrogels have the potential to significantly modify the current state of drug delivery by allowing for a more regulated and effective pharmaceutical release, enhancing therapeutic effects, and decreasing the frequency of administration. The area of biomaterials science is actively investigating the development of novel self-healing hydrogel materials and the most effective methods of using their capabilities for targeted medication administration **(He, 2020).**

4.2.1. Hydrogels that heal themselves for antimicrobial drug delivery

There is current investigation into the possibility of incorporating different medications into self-healing hydrogels **(Cai, 2020)**. For example, a self-healing hydrogel that might potentially release anti-inflammatory and anti-cancer medicines for the treatment of breast cancer was recently described in research. The hydrogel included the anti-inflammatory medicine curcumin and the anti-cancer drug doxorubicin, and it was fabricated from the biocompatible polymer poly(N-isopropylacrylamide-co-acrylic acid). Hydrogel's delayed medication release effectively suppressed cancer cell growth in vitro **(Cai, 2020).**

The biomaterials research community is very interested in the development of self-healing hydrogels that can deliver several medications with controlled release kinetics. These hydrogels may enhance the efficiency and safety of drug delivery for a variety of uses, such as cancer treatment, tissue engineering, and wound healing **(Talebian, 2019).**

4.3. Impact of Cellular Self-Repair Capabilities

When compared to standard hydrogels, self-healing hydrogels provide a variety of advantages in the field of cell therapy **(Ding, 2020).** Due to their unique qualities, including as the ability to self-repair and restore their mechanical properties after injury, they can provide the optimum environment for cell encapsulation and dispersion. For long-term cell transport to be possible, the hydrogel must keep its shape and shield the encapsulated cells from mechanical stress during implantation **(Li, 2020).**

DOI: 10.48047/INTJECSE/V14I6.369 ISSN: 1308-5581 Vol 14, Issue 06 2022

Hydrogels that repair themselves can be programmed to respond to many different stimuli, such as changes in pH, temperature, or the presence of enzymes. This feature can be used to target drug delivery or stimulate cell proliferation and differentiation by manipulating the release of cytokines and growth factors **(Talebian, 2019)**. Such hydrogels may be tailored to a variety of tissues and uses by including ligands or peptides that stimulate cell adhesion, migration, and differentiation **(Jin, 2019).**
Several research have shown that self-healing hydrogels may be used effectively to transport cells for tissue engineering and regenerative medicine applications **(Jalalvandi, 2019).** Recent research, for instance, has shown that the synthetic polymer poly(ethylene glycol)-poly(-caprolactone)-poly(ethylene glycol), or PEG-PCL-PEG, can be used to create a self-healing hydrogel that delivers mesenchymal stem cells (MSCs) for the regeneration of cardiac tissue.

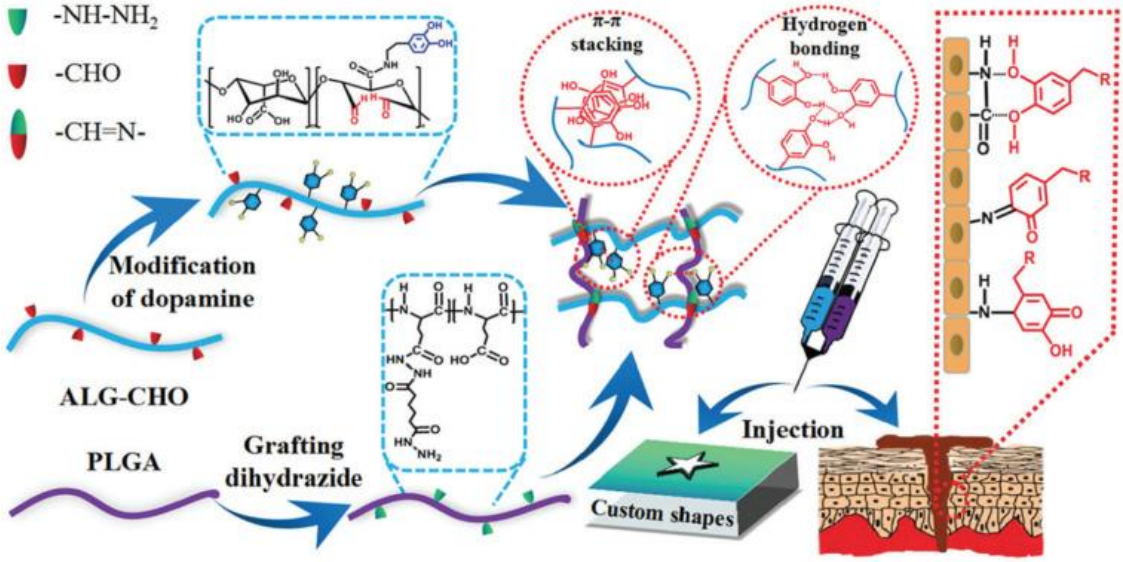

Figure 7 is a schematic of the process used to create PLGA/ALG-CHO-Catechol sticky injectable self-healing hydrogels, which were inspired by the shells of mussels.

5. Conclusions and Future Perspectives

Despite its infancy stage, self-healing hydrogel research and development has great promise. There has to be extensive research on the durability and resilience of self-healing hydrogels in physiological circumstances, especially in vivo. Novel commercial prospects may arise in the biomedical industry with the development of self-healing hydrogels that combine therapeutic and diagnostic functions. Hydrogels containing stem cells have showed promise in regenerative medicine, although there is need for improvement in this method (Li, 2020).
Even with their limitations, self-healing hydrogels have many potential biological uses because of their biocompatibility and other promising features. Self-healing hydrogels have the potential to revolutionise tissue engineering, medication delivery, and other medical fields with more study and development.

REFERENCES –

Balitaan, J. N. I., Hsiao, C. D., Yeh, J. M., & Santiago, K. S. (2020). Innovation inspired by nature: Biocompatible self-healing injectable hydrogels based on modified-β-chitin for wound healing. International Journal of Biological Macromolecules, 162, 723-736.
Cai, L., Liu, S., Guo, J., & Jia, Y. G. (2020). Polypeptide-based self-healing hydrogels: Design and biomedical applications. Acta Biomaterialia, 113, 84-100.
Chen, H., Cheng, J., Ran, L., Yu, K., Lu, B., Lan, G., ... & Lu, F. (2018). An injectable self-healing hydrogel with adhesive and antibacterial properties effectively promotes wound healing. Carbohydrate polymers, 201, 522-531.
Chen, J., Huang, Y., Ma, X., & Lei, Y. (2018). Functional self-healing materials and their potential applications in biomedical engineering. Advanced Composites and Hybrid Materials, 1, 94-113.
Chen, M., Tian, J., Liu, Y., Cao, H., Li, R., Wang, J., ... & Zhang, Q. (2019). Dynamic covalent constructed self-healing hydrogel for sequential delivery of antibacterial agent and growth factor in wound healing. Chemical Engineering Journal, 373, 413-424.

Deng, Z., Wang, H., Ma, P. X., & Guo, B. (2020). Self-healing conductive hydrogels: preparation, properties and applications. Nanoscale, 12(3), 1224-1246.
Ding, C., Tian, M., Feng, R., Dang, Y., & Zhang, M. (2020). Novel self-healing hydrogel with injectable, pH-responsive, strain-sensitive, promoting wound-healing, and hemostatic properties based on collagen and chitosan. ACS Biomaterials Science & Engineering, 6(7), 3855-3867.
Ding, C., Yang, Q., Tian, M., Guo, C., Deng, F., Dang, Y., & Zhang, M. (2020). Novel collagen-based hydrogels with injectable, self-healing, wound-healing properties via a dynamic crosslinking interaction. Polymer International, 69(9), 858-866.
He, J., Shi, M., Liang, Y., & Guo, B. (2020). Conductive adhesive self-healing nanocomposite hydrogel wound dressing for photothermal therapy of infected full-thickness skin wounds. Chemical Engineering Journal, 394, 124888.
Jalalvandi, E., & Shavandi, A. (2019). Shear thinning/self-healing hydrogel based on natural polymers with secondary photocrosslinking for biomedical applications. Journal of the mechanical behavior of biomedical materials, 90, 191-201.
Jin, J., Cai, L., Jia, Y. G., Liu, S., Chen, Y., & Ren, L. (2019). Progress in self-healing hydrogels assembled by host–guest interactions: preparation and biomedical applications. Journal of Materials Chemistry B, 7(10), 1637-1651.
Li, H., Cheng, F., Wei, X., Yi, X., Tang, S., Wang, Z., ... & Huang, Y. (2021). Injectable, self-healing, antibacterial, and hemostatic N, O-carboxymethyl chitosan/oxidized chondroitin sulfate composite hydrogel for wound dressing. Materials Science and Engineering: C, 118, 111324.
Li, S., Wang, L., Zheng, W., Yang, G., & Jiang, X. (2020). Rapid fabrication of self-healing, conductive, and injectable gel as dressings for healing wounds in stretchable parts of the body. Advanced Functional Materials, 30(31), 2002370.
Li, W., Wang, B., Zhang, M., Wu, Z., Wei, J., Jiang, Y., ... & Chen, S. (2020). All-natural injectable hydrogel with self-healing and antibacterial properties for wound dressing. Cellulose, 27, 2637-2650.
Liu, Y., & Hsu, S. H. (2018). Synthesis and biomedical applications of self-healing hydrogels. Frontiers in chemistry, 6, 449.
Ponsubha, S., & Jaiswal, A. K. (2020). Effect of interpolymer complex formation between chondroitin sulfate and chitosan-gelatin hydrogel on physico-chemical and rheological properties. Carbohydrate polymers, 238, 116179.
Talebian, S., Mehrali, M., Taebnia, N., Pennisi, C. P., Kadumudi, F. B., Foroughi, J., ... & Dolatshahi-Pirouz, A. (2019). Self-healing hydrogels: The next paradigm shift in tissue engineering?. Advanced Science, 6(16), 1801664.
Thomas, S., & Surendran, A. (Eds.). (2020). Self-healing polymer-based systems. Elsevier.
Wahid, F., Zhou, Y. N., Wang, H. S., Wan, T., Zhong, C., & Chu, L. Q. (2018). Injectable self-healing carboxymethyl chitosan-zinc supramolecular hydrogels and their antibacterial activity. International journal of biological macromolecules, 114, 1233-1239.
Wang, C., Liang, C., Wang, R., Yao, X., Guo, P., Yuan, W., ... & Xie, X. (2020). The fabrication of a highly efficient self-healing hydrogel from natural biopolymers loaded with exosomes for the synergistic promotion of severe wound healing. Biomaterials science, 8(1), 313-324.
Wang, W., Xiang, L., Gong, L., Hu, W., Huang, W., Chen, Y., ... & Zeng, H. (2019). Injectable, self-healing hydrogel with tunable optical, mechanical, and antimicrobial properties. Chemistry of Materials, 31(7), 2366-2376.
Webber, M. J., & Dankers, P. Y. (2019). Supramolecular hydrogels for biomedical applications. Macromol. Biosci, 19, 1800452.
Wei, Z., & Gerecht, S. (2018). A self-healing hydrogel as an injectable instructive carrier for cellular morphogenesis. Biomaterials, 185, 86-96.