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A Comprehensive Review on Injectable Hydrogel and it's Biomedical Applications

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ABSTRACT

The most extensively researched and adaptable smart biomaterials are injectable hydrogels (IHs), which can be introduced or implanted into living organisms with little to no disruption. These IHs show promise in a variety of biomedical applications, such as tissue engineering, regenerative medicine, implants, drug/protein/gene delivery, cancer treatment, aesthetic modifications, and spinal fusions, due to their distinct characteristics, customizable structure, and stimuli-responsive biodegradation qualities. This review provides a thorough analysis of the present status of development of a number of significant IH types, including all those that have been approved by the FDA, undergoing clinical studies, and marketed commercially. In accordance with ongoing and planned research, we also examine the structural chemistry, synthesis, bonding, chemical/physical crosslinking, and responsive release. Lastly, we also go over the accompanying future potential, difficulties, constraints, and challenges for IHs in the development, fabrication, preparation, in situ applications and regulatory affairs.

INTRODUCTION

The development of biomaterials with improved characteristics, drug-delivery capabilities, and desirable therapeutic efficacy has made it possible to treat diseases and heal wounded tissue. A hydrophilic polymer system, hydrogels are able to retain a large amount of water and swell in an aqueous solution [1-3]. However, they continue to be insoluble in water and biological fluids because of their three dimensional (3D) crosslinking structure [1,3]. Due to their extremely adsorptive surfaces, high water content, polymeric meshwork, and side chain, as well as their dynamical control over their Physicochemical properties and the release of encapsulated medication from hydrogel cores, these materials retain their well-defined designs [4].

The usual application of a hydrogel formulation starts with its early use in contact lenses and progresses to highly developed, detailed uses, mostly in tissue engineering and gene/DNA delivery for regulated and sustained medication delivery. Other common uses include bug targeting, mucoadhesive, sensors, wound healing dressing, bioactive factor administration, and cancer chemotherapy [5]. Hydrogel formulations and dosage-form preferences have been extensively researched, expanding their biomedical applications and consumer availability. Traditional intravenous medicines are losing favour to injectable hydrogels because to their numerous systemic toxicities, which include myelosuppression, liver or renal failure, non-targeted administration, prolonged/controlled release, and neuro- and other organ-toxicities.

IHs can effectively bypass these issues by releasing medications at the site of infection or tumour or at areas where there is localized drug toxicity [2,3,6]. IHs have unique hydrophilicity and biocompatibility, and possess phase transition ability -sol (liquid) to gel (solid) to form solid like gel states to administer and support medicines, genes, DNA, proteins, and cells in a sustained and regulated way through encapsulation and release [7]. They are made using a various type of mechanisms, including chemical and physical crosslinking, from natural and synthetic polymers with their respective merits and demerits [6].

CLASSIFICATION

Hydrogels were essentially divided into natural/synthetic/hybrid hydrogels, structural morphology, crosslinked hydrogels, charge (anionic, cationic, or neutral) hydrogels, biodegradable/non-biodegradable, low/high swelling or superabsorbent hydrogels,

micro/macro or super-porous hydrogels, etc. based on the nature of the material, gelation mechanism, biodegradability, side group characteristics and attachment, degree of porosity and swelling, etc. [1,3]. Through a variety of techniques, these diverse hydrogel systems have numerous applications in the biological sciences. According to their manufacturing and structural design, each has benefits and drawbacks. For example, natural polymeric materials' uncontrollable biodegradation and batch to batch variations make it challenging to regulate their mechanical strength and properties, which, in contrast to synthetic polymers, typically have a well-defined 3D structure and robustness [8-12].

Classification of injectable hydrogels:

1. **Based on source**

a. **Natural:** Agarose, alginate, chitosan, collagen, fibrin, gelatin, hyaluronic acid
b. **Synthetic**: gelatin methacryloyl, pluronic, polyethylene (PEG),polyamides, poly acrylic acid

2. **Based on crosslinking methods:**

Chemical crosslinking, physical crosslinking

3. **Based on charges:**

Anionic, cationic, amphoteric, non-ionic

4. **Based on biodegradable method**

a. **Non-biodegradable:** poly (2-hydroxy ethyl methacrylate, trimethylol-propane trimethacrylate
b. **Biodegradable natural:** collagen /gelatin, chitosan, hyaluronic acid, chondroitinsulfate, alginate, agarose, fibrin
c. **Synthetic:** polyethylene glycol, poly ethyleneoxide, poly-vinyl alcohol, poly (aldehyde guluronate), polyanhydrides.

PREPARATION AND MECHANISM OF GENNERATION:

Hydrogel Preparation and Production via chemical crosslinking (click chemistry, photo polymerization, Schiff's base, enzyme-catalysed or thiol-based Michael reactions) or physical crosslinking (induced through temperature, pH, ionic interactions, stereo complexation, or

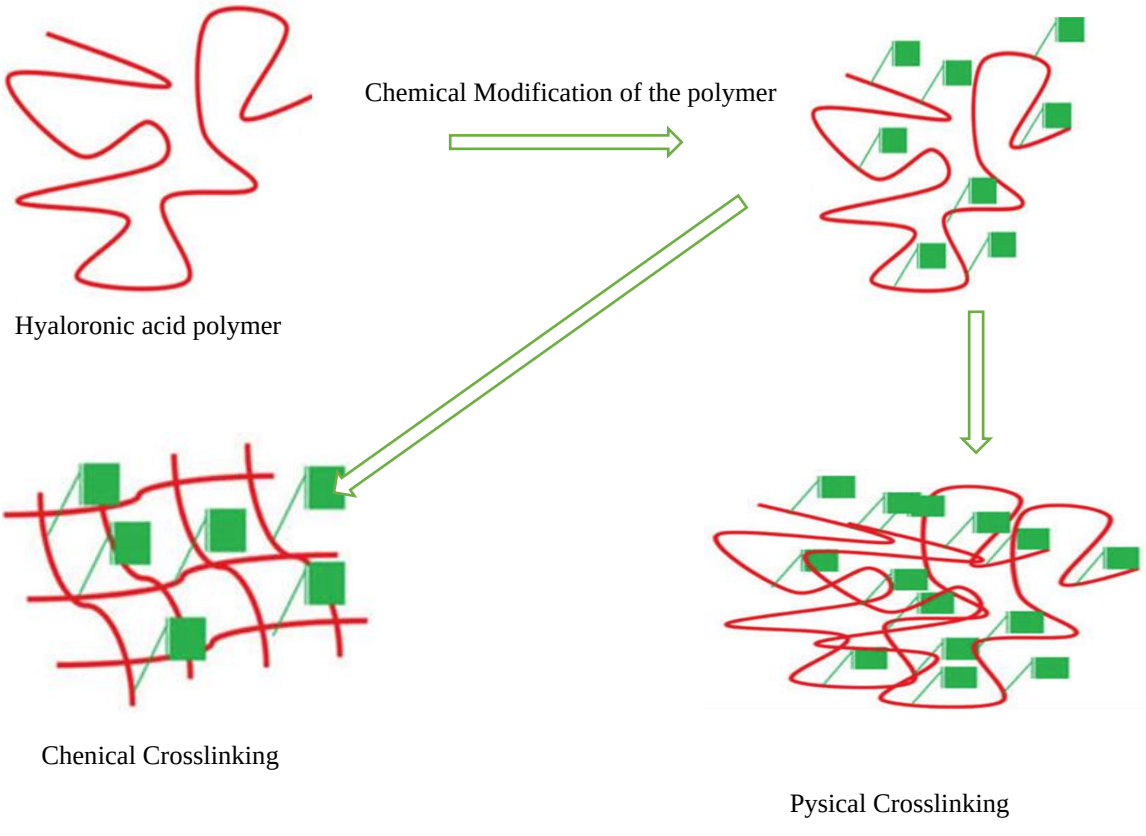
guest-host inclusion reactions), various techniques have been used to generate 3D hydrogel structures from natural or synthetic sources [9-12]. These techniques can produce hydrogels that may be used to encapsulate and release biomolecules (DNA, RNA, gene, and protein) as well as pharmaceuticals for a range of therapeutic uses [13]. When compared to hydrogels created by chemical crosslinking, IHs produced by physical crosslinking often have inferior mechanical qualities. Note that chemically crosslinked hydrogel Preparation has slow gelation kinetics, resulting in instantaneous in situ hydrogel generation upon injection. Dual-gelling hydrogels, which combine the quick gel formability of a physical gel and the mechanical strength capabilities of a chemical gel, have recently been produced [7, 14].

1. CHEMICAL CROSSLINKING

The hydrogel class that is capable of going through the transition phase, where new covalent bonds in a polymer cause it to transform from a liquid state to a gel state (sol–gel transition).

Chemically crosslinked hydrogels are meshwork created by specific chemical processes. When in-situ gels are required, they find wide use in implants and injectable devices [3,11]. Reactions that are chemically crosslinked are shown in figure.

PHOTO CROSSLINKED POLYMERIZATION



Polymers that include photosensitive molecules and polymerization catalysts (in an aqueous solution) can be used to create photo-crosslinked hydrogels. The photo-sensitive molecule decomposes polymerizes, and releases free radicals when exposed to UV/visible light (an external stimuli) systems. One such example is methacrylate (acrylate groups), which rapidly polymerizes when exposed to radiation [7]. Additionally, there are a number of benefits to photo-polymerization, including regulated gelation kinetics, patterned 3D structured hydrogels for release experiments, minimal energy requirements, no need for severe heating or local toxicity, no need for a solvent, and quick reactions under mild environments [5].

Click chemistry

Using click chemical reactions, a hydrogel three-dimensional meshwork was created by introducing azide and alkyne groups via their carbamate linkage into the chains of polyvinyl alcohol (PVA) and polyethylene glycol (PEG). This was accomplished by combining alkyne-PVA with PEG diazide or azide PVA, which can result in the formation of hydrogels. when a Cu (I) catalyst is present. It has been shown that combining these two multifunctionalized PVAs azide- and alkyne-PVA instead of employing a bifunctional crosslinker is more successful in forming gels. The crosslinking density and gelation ability improved as the functional group concentration increased.

Schiff's base reaction

Reaction between nucleophilic amines or hydrazides and Schiff's base chemical crosslink molecules, which typically include a double bond of carbon and nitrogen, can result in carbon atoms in aldehydes or ketones that are electrophilic. Under some biological circumstances, Schiff's base reactions can happen without the need for a chemical or catalyst. These qualities have drawn a lot of attention when it comes to creating and producing in-situ formed IHs, which will have a controlled reaction rate in the appropriate pH medium.

Enzyme catalysed reactions

In the presence of enzymes, enzymatically catalyzed crosslinking processes take place biologically. In order to avoid toxicity, mild reaction conditions are needed, such as an aqueous environment, neutral pH, temperature, and substrate specificity. Tyrosinase, phosphopantetheinyl transferase, transglutaminase, horseradish peroxidase, and lysyl oxidases have been utilized, especially for tissue engineering, to create hydrogels by enzyme catalysis. Horseradish peroxidase (HPR) has emerged as the most promising candidate in

enzyme-catalyzed crosslinked hydrogels because of its quick gelation, high stability, mechanical strength, and simplicity of purification [7, 15]. An HPR-catalyzed oxidative coupling of phenol components with hydrogen peroxide (H_2O_2) acting as an oxidant. The production of hydrogel systems from natural polymers like gelatin, dextran, hyaluronic acid, and chitosan has made substantial use of these oxidative catalysts which are predominately useful in tissue engineering and protein delivery [16].

Thiol- based micheal reaction

A thiol-based Michael reaction is the chemical crosslinking that occurs when the nucleophile components are thiol and amine bearing molecules, where unsaturated carbonyl components are typically attached to acrylate/methacrylate and vinyl sulfone groups. This is known as a Michael reaction that occurs when a nucleophile is added to an α- or β-unsaturated carbonyl compound. Because of their regulated reaction rate, ideal circumstances, relative inertness with biomolecules, and high percentage chemical yields, these materials find applications in biomedicine, optoelectronics, pharmaceutics, composites, coatings, and adhesives [17].

2. PHYSICAL CROSSLINKING

By altering its intermolecular forces, such as hydrogen bonding, hydrophobic interactions, and electrostatic ionic forces, physically crosslinked hydrogel can reach a gel state. It can also be obtained by complementary binding, stereo-complexation, guest-host interactions in intermolecular assemblies, etc. [18]. These alterations can be caused by the polymers' own internal organization or by external stimuli including heat, light, pH, pressure, sound, electric field, ionic strength, or the presence of certain molecules [19]. Hydrogel that has been physically crosslinked has a distinct gelation duration, mechanical strength, and biodegradation mechanism.

pH-induced

Thermal-sensitive hydrogels have limited uses in preparations due to factors such as injection blockage, lack of ionic interaction in protein, drug, or gene delivery, difficulty dissolving, and material storage. Due to these drawbacks, pH-sensitive or mixed pH/temperature-sensitive hydrogels were developed. As is well knowledge, every system in the human body has a physiological pH environment that varies. For example, the stomach (pH 1.35–3.5), liver (pH 7.6–8.8), intestine (pH 6-7.5), tumour sites (pH 6.4–7.0), blood vessels (pH 7.35–7.45),

and vagina (pH 3.8–4.5) all have physiological pH environments that can be useful for the delivery of bioactive agents to stimuli-sensitive responsive systems.

Protonation/deprotonation via an ionization constant (pKa) among ionized groups is the primary mechanism responsible for the pH-responsive phase change between soluble and insoluble.

Temperature induced

A sol gel phase transition may result from temperature induction-induced changes in the polymer's solubility and three dimensional structure. Temperature fluctuations in hydrogen production can result in fast gelation., the temperature-sensitive hydrophilic–hydrophobic hydrogels identify the macroscopic soluble–insoluble transition state in response to temperature variations in an aqueous solution. These hydrogels can be further divided into various temperature-responsive and -sensitive categories based on variations in temperature.

Ionic interactions

Ionization and deionization can produce pH-responsive hydrogels in the ion-gelation mechanism, while the opposing electrostatic ionic interactions can produce ion induced complex hydrogels.

Guest host inclusion

A supramolecular inclusion is created when chains or specific groups from guest molecules are inserted into the cyclodextrin (CD) cavity, which functions as a host molecule. This is known as physical crosslinking for guest-host inclusion, and it is complex. The host supramolecular complex shape of cyclodextrin has allowed for a wide range of applications in peptide/protein administration and ophthalmic/nasal medication delivery.

Stereo -complexation

A stereo complexation gelation method can produce a physically crosslinked hydrogel from polymers of opposite chirality. As in the case of an enantiomer, when L-lactic and D-lactic acid are combined, a PLA stereo complex is created. This selective stereo interlocking system has a higher melting temperature, mechanical strength, and hydrolytic stability than its antecedents. Many kinds of polymer pairings have stereo-complexation, however the

biodegradable poly-methyl methacrylate and non-biodegradable (poly lactic acid) interlocking is most prevalently used.

Complementary binding

Peptide-based hydrogels can be synthesized by joining complementary β-sheet subjects, β-hairpin, or assembling α-helix subjects in a coiled-coiled pattern. The self-assembling DNA hydrogels that are created by base-pairing complementary DNA strand contacts can also be made with this mechanism. Similar to this, ligand receptor interactions between growth factor/heparin, concanavalin A/glucose or antigen, and antibody binding between goat anti-rabbit IgG and rabbit IgG were utilized to create biomolecule-responsive bioconjugated hydrogels. Lastly, metal-ligand coordination between iron (II)/bipyridine, iron (III)/catechol suppressions, or nickel (II)/terpyridine was proposed for the metallo-hydrogel formation [7].

CHARACTERIZATION:

The hydrogels at the injection sites quickly transition from the sol-gel phase, enabling the matrix to readily conform to the cavity's shape and provide a good fit and interface with the tissues. Furthermore, a straightforward gel solution mixing step can be used to incorporate various medicinal compounds and even cells before injection [20]. When different functional groups of crosslinking agents are applied, the covalent bond in chemical crosslinking creates stronger ionic bonds. As a result, several polymeric structures, including homo-polymers and linear, block, or graft copolymers, are created during the polymerization process (chemical/physical). These hydrogels find applications as solid-molded contact lenses, microparticles for bioadhesive or wound dressing and treatment, tablets or capsules with confined powder matrices, coatings for catheters and implant devices, and more as liquids that gel when heated or cooled, as sheets or membranes (as a reservoir in transdermal medication patches), and as solid encapsulations (in osmotic pumps) [21,22].

Responsive Released Studies

Hydrogels that exhibit features that are susceptible to changes in external stimuli, such as swelling behaviour, structural elucidations, mechanical strength, or permeability, are referred to as "responsive stimuli" hydrogels or environmentally sensitive hydrogels. These stimuli have practical use in various controlled-hydrogel delivery systems [23]. For a variety of responsive hydrogel systems, stimuli-responsive polymers, sometimes referred to as smart polymers, can be employed. These smart polymers can be used to prepare them, or

alternatively, smart polymers can be used to modify polymer structures such that they respond to certain environmental triggers or stimuli. These external environmental stimuli could include the hydrogels' phase or collapse transitions, pH, temperature, ionic concentration, or volume changes, all of which are related to and dependent upon their swelling characteristics. The crosslinks and internal bonding that make water insoluble, enabling the achievement of correct geometrical dimensions. Hydrogels altered 3D structure and volume, together with their mucoadhesive, bio adhesive, high injectability, low toxicity, and biodegradability, make them a desirable material for tissue regeneration and medicinal delivery [23-25].

Thermosensitive

Temperature changes cause thermosensitive hydrogels to go through a sol-to-gel phase transition. A number of review publications [25-29] have lately introduced and described all of their fundamental ideas, mechanisms, and characteristics. Poly (ethylene oxide) and poly (L-lactic acid) copolymers: new thermosensitive hydrogel copolymers (PLLA) were created in 1997 by Dr. Sung Wan Kim and associates [30]. Additional thermosensitive hydrogels based on poly (N-isopropyl acrylamide) (PNIPAM) and PEO-b-poly (propylene oxide)-b-PEO (PEO-b-PPO-b-PEO) were published from their research. These thermosensitive hydrogels are based on PLLA and exhibit biodegradability and biocompatibility with extended lifespan. The material sciences have been greatly drawn to their work on thermosensitive reactions. In subsequent studies, Dr. Kim's team focused on polymers and how they gel when exposed to temperature drops, even when the temperature is raised and then drops to body temperature or room temperature. Examples of these polymers are PEO/poly (lactic-co-glycolic acid) (PLGA) and PEG/PCL, which can be used as depots for controlled insulin release [6]. Because these thermosensitive responses have a lower critical solution temperature (LCST) and spatiotemporal control over the drug release mechanism, they can effectively protect heat-sensitive medicines against degradation [4]. As a result, they have the special ability to flow freely at room temperature and solidify into a gel at body temperature. This allows for non-invasive administration of them all over the body in their liquid condition using small needle without any major surgery.

Temperature sensitive

Natural polysaccharides and thermos responsive polymers, including pluronics, can combine to create a temperature sensitive hydrogel that can go through a sol–gel process. phase change from ambient body temperature to room temperature.

These stimulus-responsive smart hydrogels' therapeutically released kinetics can be regulated by the administration site's environment or external stimuli including redox potential, low pH, illness status, or the presence of specific enzymes. In applications including therapeutic administration and tissue regeneration, these stimulus-responsive hydrogel systems can be single, dual, or multi-responsive.

pH-sensitive

Hydrogels with protonated or easily hydrolyzable bases and acids, such as amino and carboxylic groups, are referred to as pH-sensitive or responsive hydrogels when changes in the hydrogel volume are dependent on the ionic strength and pH of the surrounding environment. These groups' degree of dissociation is sensitive to changes in the external pH, which alters the concentration of internal or external ions and weakens the corresponding hydrogen in the gel. These conformational changes will cause the gel structure's crosslinking points to decrease and the hydrogel's degree of swelling to vary, which will allow the diffusion rate and drug release to be properly adjusted and controlled [23,25,28,29,31]. Let's take chitosan, for instance, which is thought to be a pH-sensitive polymer and has the ability to demonstrate dissolution via amino group protonation at pH values less than 6.2 (mild acids); at pH values greater than this, its cationic character promotes gel formation through the neutralization of repulsive electrostatic forces, electrostatic contact, or interaction with hydrophobic moieties.

Photosensitive

By adding light-sensitive moieties or chromophores, such as spiropyran, azobenzenes, o-naphthoquinone, anthracene, coumarin, and nitrophenyl, to their 3D polysaccharide structures, photosensitive light-sensitive hydrogels can be produced [24,25,27,32]. The properties of photosensitive materials allow for two different types of mechanisms to work: first, when photosensitive material is added to a temperature-responsive gel, the light energy is transformed into heat energy, raising the gel temperature to the phase transition temperature; second, when photosensitive material is added directly to the gel structure, the

ester groups break down and photosensitivity transforms the hydrophobic molecular ends into hydrophilic molecular ends, dissociating the gel at the appropriate sites for drug delivery [23].

Enzyme sensitive

Enzymes can also be utilized to measure reactivity to environmental cues or injectable hydrogel formulations. The majority of manufactured or natural polymers, as well as their crosslinking, are readily broken down by the enzymes metalloproteinase (MMPs) and hyaluronidase, which cleaves the glycosidic bonds that hold polysaccharides and polymers together. Since MMPs are function- and structure-related endopeptidases that are abundant in malignant tissues, it is known that in certain disease states, certain of these enzymes are overexpressed at the site of infection, aiding in the dissociation of His [23].

Glucose Sensitive

The skin is easily attacked and harmed by infectious agents, despite the fact that it functions as the body's defense mechanism. Additionally, due to its high healing capacity, it may not always be possible to prevent the formation of scar tissue, especially in cases where the injury is large or occurs deep within the skin (dermis/sub-dermal layers); such as in the case of burn victims or diabetic patients, where chronic wounds combined with high blood glucose levels can lead to microvascular endothelial injury and vascular diastolic dysfunction. Therefore, IHs that are sensitive to high glucose levels that is, those that carry both insulin and fibroblast L929 are the ideal type. This technique facilitates the rapid release of peptides at high glucose concentrations and permits cell proliferation within the gel matrix [32,33].

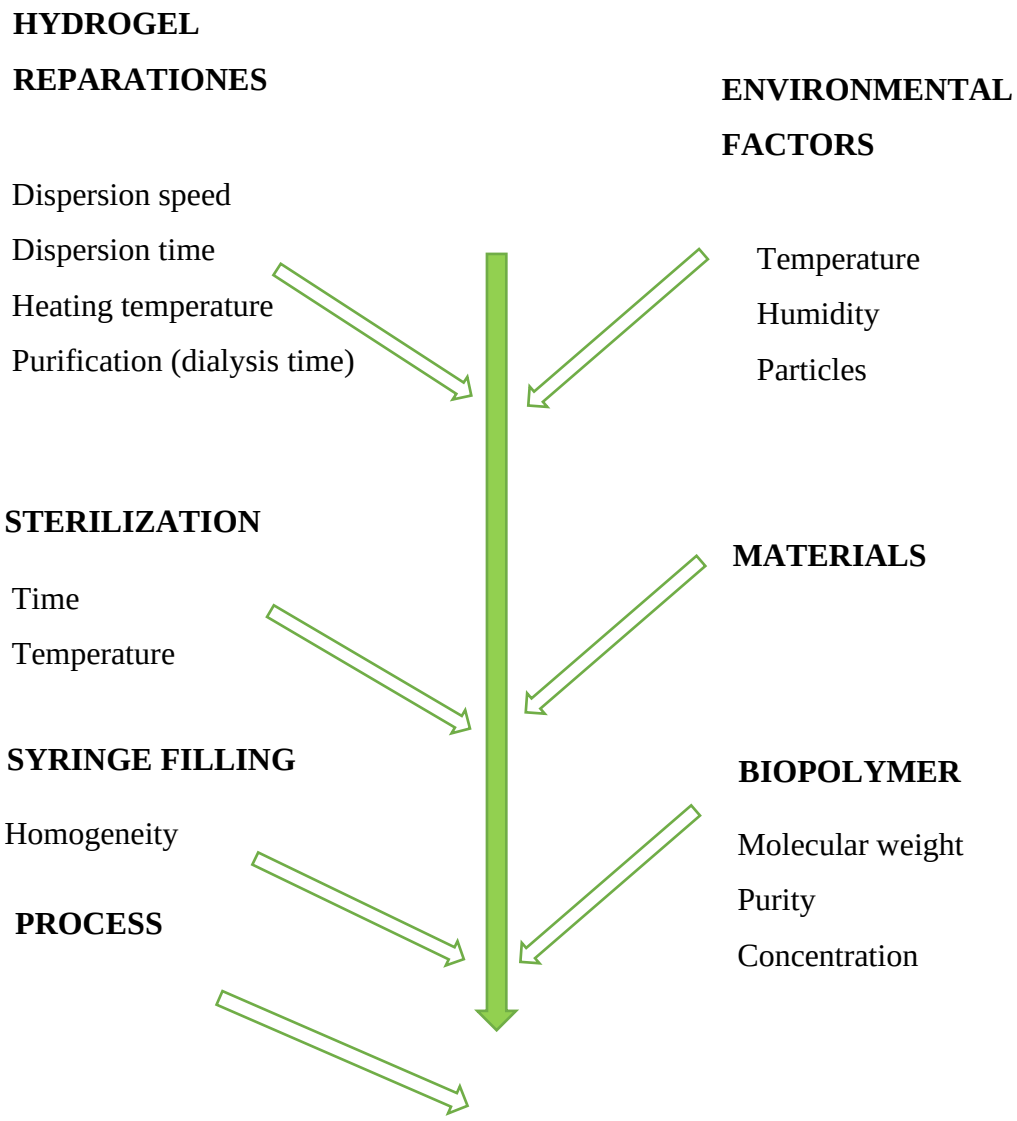


DIAGRAM FOR FABRICATION OF THE INJECTABLE HYDROGELS

THERAPEUTIC APPLICATIONS:

Tumour Immunotherapy

Immunotherapy has consistently shown promise as a cancer treatment approach and produced positive outcomes. But very few patients have actually reached optimal therapeutic results, although challenges persist when implementing it for a sizable patient population. One of the main obstacles to the widespread use of immunotherapy is still the limited immune response [34,35]. Scholars have consistently investigated novel approaches

to augment the efficaciousness of immunotherapy. The injectable hydrogel system has garnered a lot of interest since it offers the ability to regulate the release of therapeutic medications in both location and time. Currently, adoptive cell therapy, immunomodulator therapy, and cancer vaccine therapy are the three primary approaches in cancer immunotherapy.

For example, Injectable hydrogels that have been loaded with immunological adjuvants and antigens can function as powerful cancer vaccines by successfully stimulating the immune system to attract cancerous cells.

Commonly used injectable thermosensitive hydrogels have also been extensively studied as potential cancer vaccinations. A thermosensitive hydrogel based on PECE copolymers, for instance, was created by Qian and colleagues to allow for the sustained release of recombinant human basic fibroblast growth factor (bFGF) antigen [36]. After being loaded into the hydrogel, bFGF's immunogenicity was clearly enhanced. This resulted in high humoral immunity that persisted for more than 12 weeks, showing tremendous promise as a novel single-dose vaccine adjuvant for cancer immunotherapy. For the prolonged release of bFGF or GM-CSF, further thermosensitive hydrogels based on PCEC, PECE, or mPEG-PLGA copolymers have also been studied. When combined, these thermosensitive hydrogels show great potential as useful instruments for the least invasive delivery of cancer vaccines. Apart from the thermosensitive hydrogels, DNA-based hydrogels could also be a well-liked and effective vaccine delivery platform [37]. Immunostimulatory injectable DNA-based hydrogels comprising TLR9 agonist, unmethylated CpG, and ovalbumin (OVA) model antigen were developed by Nishikawa and colleagues [38]. Clearly, these suggested CpG DNA hydrogels demonstrated a more effective immune adjuvant delivery capacity when compared to other injectable hydrogels.

Injectable hydrogels on wound healing

They are artificially created to maintain, enhance, and regulate angiogenesis. Photothermally sensitive hydrogels can be used to change parameters such as cycle time, photothermal-initiator concentration ratio, and NIR irradiation intensity time. Raising the temperature from over 50°C can effectively stop the growth of bacteria, and between 41°C and 43°C, wound closure and healing can be accelerated. Under near-infrared radiation, copper nanoparticles (NPs) in gels (GelMA/BACA-Cu) have good photothermal capabilities. Hyperthermia (>55 °C) can effectively suppress bacterial growth after ten minutes of exposure to NIR, and its

antibacterial action can be further enhanced by the addition of Cu2+. Compared to the control group's 79% wound closure rate, the NIR + GelMA/BACA–Cu NPs hydrogel group's rate was 95%. It also has a significant impact on the promotion of fibroblast proliferation and angiogenesis.

Chu and colleagues created an NIR + Cu carbon dots biomaterial. Following a 14-day treatment period, the biomaterial's wound closure rate was 96% (compared to 62% in the control group). Additionally, H&E staining revealed increased collagen depositions, neovascularization, and re-epithelization in the biomaterial compared to the control group. When NIR-induced hyperthermia is halted, the residual pathogens cannot be effectively suppressed because of its short-term antibacterial activity. Consequently, some research has proposed the encapsulation of antibiotics in combination medicines as a way to overcome these difficulties.

Bone regeneration

Temperature conjugation based on alginate to create bioconjugate-injectable scaffold systems that can speed up bone biomineralization, phosphorylation functional groups (PCLA-b-PEG-b-PCLA-/Alg) such as -responsive poly(ε-caprolactone-co-lactide)-b-poly(ethylene glycol)-b-poly(ε-caprolactone-co-lactide) and O-phosphoryl-ethanolamine can be employed [39]. These bioconjugates displayed a sol gel transition when heated from ambient temperature to physiological temperature. The XRD examination verified that the bioconjugate hydrogel could cause a decrease in crystalline hydroxyl apatite in both in vitro and in vivo biomineralization. Additionally, it released BMP-2 (mitogenic factors) for a duration exceeding three days. The presence of calcium deposition at the eroded areas in these BMP-2-containing PCLA-b-PEG-b-PCLA/Alg bioconjugate hydrogels indicates mineralization and bone repair [40].

Future prospects

Many natural and synthetic hydrogel systems, like the previously mentioned thermosensitive hydrogels, are free-flowing sols at low temperatures; however, when they reach body temperature, or physiological temperature, they transform into stable visco-elastic gel phases, like poly (phosphazene), pluronic, and poly (N-isopropyl acrylamide). To get over these restrictions, poly (ester)-based copolymers are a good substitute, but further investigation is still needed. Furthermore, local drug-carriers such as PEG and poly(ester)-based hydrogels

are ineffective for long-term treatments. The FDA has cleared them for in vivo implantation, but their oral and nasal route administrations are inappropriate. Future problems also face injectable hydrogels, which are used for controlled delivery of proteins and peptides, chemical interactions, compatibility of structure, and burst release (when charged proteins are introduced to uncharged formulations) [39].

TYPE OF HYDROGEL INJECTABLE MATERIAL	CHEMICAL/ PHYSICAL CROSSLINKING	APPLICATION AND ADVANTAGES	LIMITATIONS	REFERENCE
Hydrophilic monomer and hydrophobic comonomers	Hydrophobic interaction	Absence of crosslinking agents and relative ease of production	Poor mechanical characteristics	[41]
Solution and multivalent ions of opposite charge	Ionic interaction	Crosslinking takes at RT and physiological PH can be fine-tuned by cationic and anionic constituents	Limited to ionic polymers and sensitive to impurities	[42]
Polymeric functional groups of high electron density with electron deficient hydrogen atom	Hydrogen bond	Increase in polymer concentration can increase the stability of gel	Influx of water can disperse /dissolve the gel within short duration	[43]
Hydrophilic monomers,initiators,-linkers and suspending agent	Suspension polymerization	Directly usable as powders, beads or microspheres restricted to water-insoluble polymer	Cooling jacket required to dissipate heat requirement of agitators and dispersant	[44]
Viny polymers, initiators and crosslinking agents	Grafting	Improve functional properties of the polymer	Difficulty of characterizing side chains	[45]
High energy gamma beams and electron beams as initiators	Irradiation	Does not require catalyst and other additives	Irradiation can cause polymer degradation	[46]
Bi or multifunctional monomers and each with attest two sites for bonding	Step growth polymerization	No initiator is required to start the polymerization and termination reactions	Prolonged reaction times required to achieve a high degree of conversion and high molecular weights	[47]

HYDROGEL GEL BASED COMMERCIALLY AVAILABLE PRODUCT

BRAND/ COMMERCIAL PRODUCT	ACTIVE CONSTITUENTS	DOSAGE FORM	APPLICATION	MANUFACTURER	POLYMER
Iluvien	Fluocinolone acetonide	Intravitreal implant	Treatment of diabetic macular edema	Alimera sciences,Alpharetta, Georgia	Polyvinyl alcoholand silicone adhesives
Yutiq	Fluocinolone acetonide	Intravitreal implant	Treatment of chronic non infectious uveitis affecting the posterior segment of the eye	Eyepoint pharmaceuticals the Massachusetts,USA	Polyvinyl alcohol
Ozurdex	dexamethasone	Intravitreal implant	Macular edema, non-infectious uveitis	Allergan ,California, USA	Poly (D,L-lactide-co-glycoid)
Viniferamine wound hydrogel Ag	Silver	Infective wound dressing	Partial and full thickness wounds with signs of infection and little to no exudate	McKesson, Texas, USA	Glycerin Metallic silver
CMC fiber dressing	Nil	Wound dressing	Absorptive dressing for moderate to heavy exudate	Gentell, Pennsylvania, USA	Carboxymethyl cellulose
Inadine™ (PVP-1) non-adherent dressing	Povidone iodine	Wound dressing	Ulcers deriving from different etiologies, chronic wounds	3M Health Care Ltd., Minnesota, USA	Polyethylene glycol

INJECTABLE HYDROGEL APPROVED BY FDA

A few commercially available in situ IHs that have received FDA approval. Notes are made regarding the brand name, FDA approval status, injection type, polymer type, gelation mechanism, and indications.

BRAND NAME/ COMPANY	GELATION MECHANISM	INJECTION TYPE	APIS	HYDROGEL MATERIAL (TYPES)	INDICATIONS
Zyplast(R)® and Zyderm(R)® (Inamed Corporation/Allergan, Inc., California, USA)	Chemical reaction	Dermis	Bovine	Bovine collagen	For correction of contour deficiencies
Sandostatin® Novartis Pharm. Corp., Basil, Switzerland)	Physical interaction	Dermis		Collagen (Natural)	For correction of depressed cutaneous scars
Atrisorb D® Atrix Lab. Inc., London, UK	Temperature		Doxycycline hyclate	PLGA	Periodontal tissue regeneration
Osteogenic protein 1(OP-1®) implant, OP-1® Putty (Stryker Biotech, Michigan, USA)	Physical interaction	Spinal injection		Collagen, carboxymethylcellulose, and recombinant OP-1 (Natural	Posterolateral lumbar spinal fusion

Injectable Formulation Challenges

IHs share certain noteworthy concerns with their specialized applications and need to be further investigated. Protecting DNA, peptides, proteins, and oligonucleotides from enzymatic degradation or denaturation requires that the fragile molecules or cells be compatible with hydrogel crosslinking and maintain their proliferation in a healthier environment. Understanding cytotoxicity and inflammatory reactions and how they interact with surrounding tissues and cells is important for preventing them. Low reproducibility, poorly defined structures, and employed system considerations that should be properly taken into account include the release profile of bioactive factors, the degradation period, the mechanical sturdiness after gelation, the rate kinetics, and viscosity during the injection time [48]. It should be mentioned that these IHs need to have biological computability and chemical-physical crosslinking with application specific design metrics that are responsive to certain ailments or etiology [49, 50].

Mechanical Robustness

One of the main design challenges is to maintain a low viscosity and sustainability of enough elasticity in situ for repeated load and volume [20]. Since a needle and syringe are used to administer these hydrogels, in situ gelation and repeated dosages are quite concerning. An injectable is replacing shear thinning polymers, like hyaluronic acid, which are currently utilized as a dermal filler to replace cartilage [2,14,50]. Therefore, the elastic modulus has an inverse relationship with the molecular weight of the polymer, whereas the chains, degree of crosslinking, crosslinking method, and viscosity have a linear relationship with the molecular weight [15,49].

Loading and Release of Therapeutic Agents

Through IH carriers, which have corresponding physicochemical properties, therapeutic agents, such as tiny drug molecules, macromolecules (peptides, proteins, nucleic acid, etc.) or living cells, can be loaded and released into the surrounding environment. The size, affinity, and interactions between the cargo and the gel control their effective release. At the moment, microparticle depot systems (small molecules or biologics) are used as IHs in clinical practice. The most widely accessible depot formulations include the anesthetic drug lidocaine, along with several injectable hyaluronic acid hydrogel products that are licensed for use in facial cosmetic procedures. The rapid release of lidocaine from hydrogel meshes causes disruptions in its release. Likewise, it's essential to elute additional medications from hydrogel formulations for the prolonged release of proteins and/or medications in wound dressings. To improve the retention period of the solute or to stir up its elution, the hydrogel mesh size in these formulations should be reduced by physical or chemical crosslinking [41].

Bioactivity of Hydrogel

For the objective of tissue regeneration, bulk hydrogel materials must be penetrated, changed, and broken down. Hyaluronic acid, fibrin, or gelatin are examples of manufactured or natural adhesive compounds that cells or growth factors must adhere to in order for hydrogel bioactivity to occur. These bioactive hydrogels create an appropriate cell-adhesive milieu that speeds up the healing of renal or myocardial tissue injuries. To promote cell adhesion and penetration, adhesive ligands must be chemically added to some non-adhesive polymers, like polyacrylamide and PEG. On the other hand, the fast biodegradation of some commercial hydrogels, including TraceIT®, which targets tumor margins, is a design restriction. A

polymer hydrogel that breaks down gradually over weeks to months must therefore be used, or substituted [1,15,51,52,53].

The Compatibility of Immune Systems

In recent decades, there has been a significant amount of research focused on inducing immune responses to IH biomaterials. Therefore, during in situ gel transitions, it is crucial to reduce all forms of immune reactions in injectable hydrogel formulations [54,55]. Inflammatory cascades, fibrosis, and hypersensitivity reactions are among the immunological reactions that are thought to be the worst effects of biomaterial injection, insertion, and implantation. According to research, these reactions have negative effects on the performance, function, and future applications of hydrogel materials. They are also linked to physico-chemical shifts and responsiveness (i.e. changes in the local pH or temperature) [56]. Therefore, a crucial biological design criterion is minimizing IH-associated host-immune reactions. Immunocompatibility, immune escape, prolonged release, and sustained release can all be achieved with cell-based drug delivery systems (erythrocytes, leukocytes, platelets, cancer cells, and hepatic cell membrane biomimetic nanosystem fabrications) [57-69]. These cell-based biomimetic nanosystems have been produced using a variety of hydrogels [70].

Regulatory Approval

As we previously discussed, the FDA approval process and regulatory affairs are drawn-out procedures that require years to complete, ranging from laboratory synthesis to market launch and surveillance. The variety of injectable hydrogel scaffolds and the range of crosslinking polymers and biomaterials that are used make it difficult to classify and approve them legally [15].

GMP Procedures and Scale-Up Strategies

For the clinical translation and integration of biomaterial-based hydrogels in large-scaled systems and their compatibility, current good manufacturing practices (cGMP) are necessary, since the majority of hydrogel systems are developed and manufactured at a small pilot-plant scale during pre-clinical stages.

CONCLUSION:

Considering all of the facts of IHs, it is evident that much more investigation and study are still required for their potential uses in medicine. Their creative potential appears to have the

potential to provide new knowledge and revolutionary advances, particularly in the areas of biomedical engineering, tissue regeneration, drug, protein, and gene delivery, cancer chemotherapies, wound dressings, implants, and the targeting of superbugs. The use of hydrogels is expanding due to various factors such as FDA-approved formulations, crosslinking modules, biomedical applications, molecular-level studies, and natural, synthetic, and natural-synthetic hybrid synthesis; these developments will also broaden the therapeutic applications of hydrogels in other health conditions and complications. This means that by drawing attention to all these drawbacks, their disadvantages, and the design difficulties with injectable formulations, future research into more creative and effective uses will be made possible.

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