

REVIEW ARTICLE

Injectable Hydrogels for Biomedical Applications: A Review of the Current Clinical Landscape

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Abstract

Injectable hydrogels are gaining popularity due to their diverse biomedical applications, including tissue engineering, dermal fillers, drug delivery, and regenerative medicine. An ideal injectable hydrogel should have suitable physicochemical properties for in situ injection into the body, be non-toxic and biocompatible, and should not initiate any adverse reactions. Also, the injectable hydrogel should be porous and made of highly interconnected networks to facilitate the movement of nutrients for better integration into the surrounding tissues. Injectable hydrogels offer unique advantages such as minimally invasive delivery and targeted administration, making them promising candidates for various medical interventions. The preparation of injectable hydrogels involves physical or chemical crosslinking methods, and various stimuli-responsive injectable hydrogels are available for clinical use. Optimising their composition, distribution, and dosing regimens is key to enhancing patient outcomes and expanding the clinical utility of injectable hydrogels shortly. There are various injectable hydrogel products in the market, and a few of them are in different phases of clinical trials for treating several diseases and conditions. Examples of commonly used injectable hydrogels available in the market include hyaluronic acid, calcium phosphate, collagen, fibrin, and thermoresponsive hydrogels. Furthermore, ongoing clinical trials investigating novel injectable hydrogels such as BioSentry tract sealant system, PROMGEL-OA, HYADD, PAAG-OA, NOLTREX, AQUAMID, GELSTIX, and REACT are discussed in this review, providing valuable insights into the landscape of injectable hydrogel research and development. In this review, we primarily focus on injectable hydrogels under various stages of clinical trials for future addition to the clinical setting, and some of the products approved for clinical use. It also examines the current clinical landscape of injectable hydrogels for biomedical applications, highlighting their versatility in tissue engineering, drug delivery, and wound healing. While approved products promise conditions like osteoarthritis, ongoing clinical trials underscore the need for further research to assess safety, efficacy, and long-term outcomes, suggesting significant potential for transformative advancements in healthcare.

Keywords: Injectable Hydrogels; Clinical Trials; Tissue Engineering.

1. Introduction

Hydrogels are three-dimensional polymeric networks that can absorb and retain large amounts of water. The injectable hydrogels, due to their versatile nature and ease of deliverability, make them a potential candidate for applications in tissue engineering [1, 2], regenerative medicine [3], drug delivery [4], and localized cancer therapy [5]. Allied Market Research projected that the hydrogel market is expected to fetch \$15.3 billion by 2025. The use of conventional hydrogels in the form of patches or bulk requires surgical implantation, which raises the possibility of inadequate target site adaptation and post-surgery infections. On the other hand, the injectable hydrogels that are administered through a less invasive technique offer enhanced flexibility, which lowers the probability of infection and scarring [6, 7]. Biomedical research can benefit from the varied applications of injectable hydrogels in an array of fields, including medication delivery and tissue engineering. They function as injectable scaffolds in tissue engineering, imitating the extracellular matrix and creating an environment that is favorable for cell proliferation and tissue regeneration. Hydrogels can encapsulate biomolecules, growth factors, and cells, allowing for their controlled release at the site of injury to promote regeneration of tissue and wound healing [8, 9].

Physical and chemical hydrogels are the two groups of injectable hydrogels. Non-covalent interactions between the polymer chains, such as hydrogen bonding and van der Waals forces, result in the development of physical hydrogels. Because they are reversible, the gel can be dissolved and reformed without changing the polymer chains' chemical structure [10]. These hydrogels have a number of benefits, including biocompatibility, biodegradability, and ease of manufacture. Physical hydrogels exhibit several drawbacks, too, such as quick rates of deterioration and poor mechanical strength. Covalent cross-linking between the polymer chains creates chemical hydrogels. They are perfect for load-bearing applications because of their tunable mechanical qualities and stability [11]. Chemical hydrogels also offer longer-term stability than physical hydrogels because of their slower rates of breakdown. Chemical hydrogels, on the other hand, can be more challenging

to make and might need harmful cross-linking agents [12, 13].

In the clinic, hyaluronic acid hydrogels are frequently utilized for a number of purposes, such as treating osteoarthritis and as dermal fillers. Synvisc-One is a recognized hyaluronic acid hydrogel that is used to treat osteoarthritis in the knee [14]. The scarred cartilage is lubricated and has stress absorption properties thanks to the injection of the hydrogel directly into the joint. For dermal filler treatments, other hyaluronic acid hydrogels, like Restylane and Belotero Balance, are used to minimize the appearance of wrinkles and fine lines [14]. In the clinic, calcium phosphate hydrogels are utilized for bone regeneration purposes. In order to create a scaffold for cells to develop and differentiate into bone tissue, these hydrogels—which consist of calcium phosphate particles and a polymer matrix—are injected into the exact area of the bone defect. A calcium phosphate hydrogel that's now being used in clinical settings is BonAlive® putty, which is authorized for usage in both Europe and Asia [15, 16].

Injectable hydrogels based on collagen are frequently utilized in clinics for wound healing purposes. As injectable hydrogels based on collagen and fibrin may replicate the extracellular matrix (ECM) found in the natural wound healing manage, they are widely used in wound healing applications. Collagen, a key element of the extracellular matrix and a natural scaffold for cell growth and regeneration makes up these hydrogels. Excellagen is one type of collagen-based hydrogel that is now being used in clinical settings to treat diabetic foot ulcers. Injecting the hydrogel into the wound site creates a scaffold on which cells can proliferate and move, facilitating tissue regeneration [17]. Platelet-rich Plasma (PRP) hydrogels are concentrated platelets high in growth factors that are made from the patient's blood. To decrease inflammation and promote tissue regeneration, they are injected into osteoarthritic joints. PRP hydrogels can also be applied as dermal fillers to rejuvenate the face by enhancing the texture of the epidermis and promoting the production of collagen [18]. Polymethyl Methacrylate (PMMA) Microspheres in a collagen matrix for dermal filler operations. PMMA microspheres encapsulated in a collagen matrix serve as injectable implants. By stimulating collagen formation surrounding the

microspheres, this combination produces long-lasting volume augmentation and long-lasting esthetic improvement. Calcium Hydroxyapatite Hydrogels (CaHA) are biocompatible fillers called CaHA hydrogels utilized in dermal filler treatments as well as the treatment of osteoarthritis. They stimulate tissue regeneration and offer physical support in cases of osteoarthritis [19].

Hyaluronic Acid (HA) Hydrogel is a naturally occurring polysaccharide that is present in connective tissues. In orthopedics, injectable HA hydrogels are frequently used to treat osteoarthritis by lubricating and cushioning the joint area. Biodegradable and wound-healing, fibrin hydrogels are derived from fibrinogen found in blood plasma. They are applied as sealants in surgery and for tissue restoration in regenerative medicine [20]. Gelatin methacryloyl (GelMA) hydrogels have outstanding properties for cell attachment and proliferation. They are used in localized medication delivery and 3D bioprinting to create tissue constructions. Calcium Alginate hydrogels encapsulate cells for controlled management. Calcium Alginate hydrogels, which are created by crosslinking alginate with calcium ions, are used in tissue engineering and wound healing applications [21].

Polyethylene Glycol (PEG) hydrogels have flexible characteristics and are biocompatible. Because of their regulated release kinetics, they are used as medication delivery vehicles and in tissue engineering for cell encapsulation. In the clinic, injectable hydrogels based on fibrin are also utilized for wound-healing purposes. A soluble precursor of fibrin, fibrinogen is essential to the cascade of blood clotting. Fibrinogen is converted enzymatically into fibrin to produce fibrin hydrogels, which act as an interim structure for cell adhesion and migration during wound healing. Fibrin hydrogels that can be administered stimulate hemostasis, hasten wound healing, and enhance tissue regeneration [22]. These hydrogels are useful for tissue engineering, surgical wound closure, and wound healing in chronic conditions, including pressure sores and venous ulcers. The natural blood clotting system components fibrinogen and thrombin make up these hydrogels. These elements interact when injected into the wound site to create a fibrin network that acts as a scaffold for the growth and regeneration of cells. Artiss is one fibrin-based hydrogel that is being used in medical

procedures for surgical tissue bonding [23, 24]. The Figure 1. shows the schematic diagram displaying the various applications of injectable hydrogels.

As thermoresponsive hydrogels harden at body temperature, injectable applications can benefit greatly from their use. GelrinC, a thermoresponsive hydrogel utilized in cartilage regeneration, is one example of a hydrogel currently in clinical usage. Once injected into the cartilage defect site, the hydrogel hardens when exposed to a slight temperature increase, taking on the shape of the defect and acting as a scaffold for the growth and regeneration of cells [25]. Recent years have seen notable advancements in the clinical usage of injectable hydrogels, with multiple formulations being licensed for treatment in a range of medical ailments. These hydrogels' success in clinical trials has opened the door for their usage in the clinic. They have demonstrated promise in tissue engineering, drug delivery, and wound healing applications [26, 27].

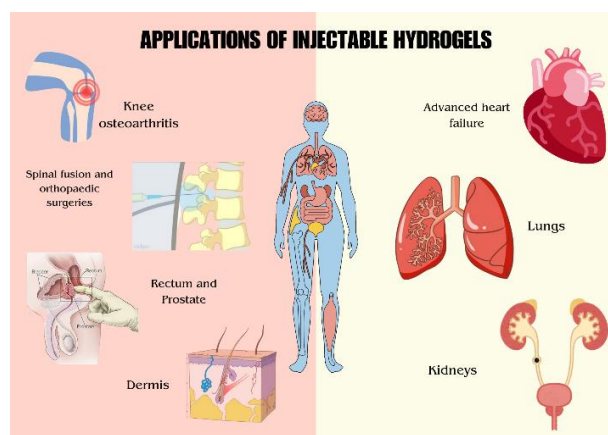


Figure 1. Schematic diagram showing the various applications of injectable hydrogels

Injectable hydrogels have the potential to completely change how a wide range of medical problems are treated with further study and development. With advancements in various technologies and techniques for the preparation of injectable hydrogels, there is a considerable number of products for treating various diseases and conditions in healthcare. In this review, we mainly focus on the injectable hydrogel products which are approved for clinical use, and we will see a bunch of injectable hydrogels under clinical trials for further addition to the health care setting.

2. Materials and Methods

The ongoing clinical trials of various injectable hydrogels dated were obtained from clinicaltrials.gov dated December 27th, 2023, using the keyword “injectable hydrogels,” and the active clinical studies are reviewed.

3. Some of the Injectable Hydrogels Available in the Market

3.1. Euflexxa®

EUFLEXXA is a bacterial cell extract that has been thoroughly purified. It is a polymer made up of a repeating N-acetylglucosamine and sodium glucuronate disaccharide linked by alternating Pf-1, 4 glycosidic linkages. Injections into the joint are known as intra-articular injections. It is most typically used to treat hip and knee osteoarthritis [28]. Patients who have not found relief from traditional analgesics and non-pharmacologic therapies for knee osteoarthritis can use EUFLEXXA [29]. Table 1 provides information on the few injectable hydrogels that are currently available in the market.

3.2. Infuse®

Infuse is a breakthrough FDA-approved bone transplant that promotes natural bone development and remodelling without needing bone harvesting from other body sections. Recombinant human Bone Morphogenetic Protein-2 (rhBMP-2), called Infuse received approval for use in a number of trauma, dentistry, and spine applications. In the INFUSE Bone Graft, rhBMP-2, which is known as Dibotermis alfa is inserted on top of a collagen absorbable sponge. At the location of implantation, it promotes the growth of new bone tissue [30]. According to data from non-clinical testing, the implant's bone production process progresses from the implant's outside to its inside until trabecular bone completely replaces the entire device [31, 32].

3.3. Algisyl-LVR® Hydrogel Implant

In patients with dilated cardiomyopathy having open-heart surgery, Algisyl-LVR was used to augment

the left ventricle. During the surgical operation, Algisyl-LVR will be injected directly into the myocardium under direct vision. The hydrocolloid alginate is elastic and irreversible. Direct restorations and permanent hydrocolloid impressions are tightly related. Alginate impressions are a simple, cost-effective, and necessary aspect of dental practice. The treatment involves sticking a needle into an artery, vein, or other blood vessels until a flow occurs. The starting point is then defined by the addition of a flexible "introducer guide wire" through the skin and into the blood artery lumen [33, 34].

3.4. Radiesse®

Synthetic calcium hydroxylapatite suspended in a gel of sterile injection sodium carboxymethyl cellulose, glycerin makes up the majority of the RADIESSE injectable implant. It is a cohesive, semi-solid, opaque, sterile, and non-pyrogenic implant. Radiesse increases volume to the hands for a short time to help restore volume loss. In addition to being approved for use on the hands, Radiesse is suggested for subdermal implantation to treat any sort of facial creases and folds, including the nasolabial fold. Through subdermal implantation, nasolabial folds and any other sort of facial wrinkles and folds are treated using the injectable implant RADIESSE. Additionally, it is used to reverse and repair the signs of lipoatrophy (loss of facial fat) in those who have the human immunodeficiency virus. Nasolabial folds and other any sort of facial wrinkles and folds can be reduced using the dermal fillers RADIESSE [9, 35].

3.5. Belotero Balance®

BELOTERO BALANCE is a clear, colorless, homogenous, viscoelastic, sterile, bioresorbable, and non-pyrogenic device that is made of gel. After being cross-linked twice with the binding substance 1,4-butanediol diglycidyl ether, hyaluronic acid from streptococcal cultures is reconstituted in a physiological buffer at pH 7. BELOTERO BALANCE is an injectable, dermal filler made of hyaluronic acid and fermented by bacteria. A concentration of 22.5 mg/mL. The needle will be placed at a roughly 300-degree angle to the length of the wrinkle or folds using the liner threading and tunnelling processes. The mid-to-deep dermis should

Table 1. Some of the injectable hydrogels available in the market

Product name/Approving agency (year)	Company	Material	Injection type	Applications
EUFLEXXA®/FDA (2004) EMA (2005)	Ferring Pharmaceuticals Inc.	Hyaluronic acid	Intra-articular	Knee osteoarthritis
INFUSE® bone graft/ FDA (2002)	Medtronic Inc.	Collagen and recombinant human BMP-2	Spinal	Spinal fusion and orthopaedic surgeries
Algisyl-LVR® hydrogel implant/ EMA (2014)	Lone StarStar Heart Inc.	Alginate	Percutaneous	Advanced heart failure
Radiesse® / FDA (2015)	Merz Pharmaceuticals	Hydroxylapatite and carboxymethyl cellulose	Dermis	Repair of volume loss in the backs of the hands and smoothing out of facial creases and folds
Belotero balance®/ FDA (2019)	Merz Pharmaceuticals	Hyaluronic acid with lidocaine	Dermis	Smoothing of moderate, really deep facial wrinkles and folds
Revanesse® Versa/ FDA (2017)	Prollenium Medical Technologies Inc.	Hyaluronic acid	Dermis	Treat moderate to severe facial folds and wrinkles, including nasolabial folds
Teosyal® RHA/ FDA (2017) EMA (2015)	Teoxane S A	Hyaluronic acid	Dermis	Treat facial wrinkles and folds
Vantas®/ FDA (2004) EMA (2005)	Endo Pharmaceuticals	Poly(2-hydroxyethyl methacrylate), poly(2-hydroxypropyl methacrylate) and histrelin acetate	Sub-cutaneous	Treatment for prostate cancer by lowering the sex hormones
SpaceOAR® Hydrogel/ FDA (2015) EMA (2010)	Augmenix, Inc.	Polyethylene glycol	Percutaneous	Spacer between rectum and prostate during cancer radiotherapy
TraceIT® Hydrogel Tissue Marker/ FDA (2013)	Augmenix, Inc.	Iodinated polyethylene glycol	Percutaneous	Improve the target definition in radiotherapy, thereby reducing the radiation doses.
Bulkamid® Hydrogel/ EMA (2003) FDA (2006)	Searchlight Pharma	Polyacrylamide	Transurethral	Mixed urinary incontinence and stress management
Coaptite®/ FDA (2005) EMA (2001)	BioForm Medical, Inc.	Glycerin, calcium hydroxylapatite, and sodium Carboxymethylcellulose	Submucosal	Management of stress urinary incontinence in females

be injected with BELOTERO BALANCE. Consistently applying low to moderate plunger pressure and gradually withdrawing the needle is sufficient to complete the injection. There should not be much blanching or skin elevation. Avoid injecting BELOTERO BALANCE into the superficial dermis after withdrawing the needle to avoid apparent lumps and discolouration. It is also used to treat moderate-to-severe facial wrinkles and folds, including nasolabial folds, by injecting it into the mid-to-deep dermis [36].

3.6. Revanesse® Versa

Revanesse Lips+ is a sterile, biocompatible, biodegradable, non-pyrogenic, viscoelastic

transparent hydrogel that contains 0.3 percent lidocaine. Streptococcus bacteria are responsible for the production of Hyaluronic Acid (HA). A pre-filled disposable glass syringe is used to administer the gel. Each syringe comes with a finger grip, a plunger rod, a rubber stopper tip cap, and a luer lock adaptor. Each Revanesse Lips+ carton contains two 1.0 mL Revanesse Lips+ syringes and two 0.5-inch 30-gauge sterile needles. For the treatment of any sort of facial wrinkles and folds in adults 22 years of age and older, an injection into the mid to deep dermis is utilized to treat areas like nasolabial folds [37].

3.7. Teosyal® RHA

It is constructed with sterile, biodegradable, viscoelastic hyaluronic acid (HA) that has been cross-linked. It utilizes a novel method that attempts to lower the degree of modification (MoD) of HA in the finished product while decreasing HA chain disintegration throughout the production process to improve flexibility to skin movements. Natural HA polymers are protected from crosslinking-related cleavage under these improved manufacturing circumstances. Fewer 1,4-butanediol diglycidyl ether (BDDE) covalent connections can be used to maintain the network of entangled HA fibers created by the high molecular weight chains. Hyaluronic acid is a chemical that naturally occurs in the fluids of the joints and eyes. The tissues around the joints serve as a lubricant and a cushion. Several different types of hyaluronic acid are utilized in cosmetics. Hyaluronic acid injections are permitted by the United States Food and Drug Administration to treat a variety of conditions, such as osteoarthritis and cataracts, as well as to treat facial wrinkles with Juvéderm, an injectable gel filler. Hyaluronic acid is frequently ingested and administered topically to treat a wide range of conditions, including urinary tract infections (UTIs), acid reflux, dry eyes, wound healing, aged skin, and other conditions; however, most of these other treatments lack scientific support [38].

3.8. Vantas®

The VANTAS (histrelin acetate) implant is a sterile, non-biodegradable hydrogel polymer reservoir that contains histrelin acetate, a synthetic nonapeptide version of naturally occurring gonadotropin-releasing hormone (GnRH). The sterile VANTAS implant has a cylindrical hydrogel polymer reservoir of 3.5 cm by 3 mm, a 50-mg histrelin acetate medication core. The color of the implant can range from off-white to light brown, and it might appear partially to fully. Within the center, the color may be irregular. The inactive component stearic acid NF is also present in the medication core. The hydrogel polymer reservoir is a hydrophilic cartridge made of benzoin methyl ether, Perkadox-16, trimethylolpropane trimethacrylate, 2-hydroxyethyl methacrylate, and 2-hydroxypropyl methacrylate. This implant is pre-programmed to release the medication as soon as it is implanted. The

implant may be inserted into the upper arm's tissue beneath the skin of the inside, utilizing the provided single-use, sterile insertion tool [39, 40].

3.9. Spaceoar® Hydrogel

to lessen the radiation dosage delivered to the rectum during radiation therapy, SpaceOAR Hydrogel is designed to temporarily separate the prostate from the rectum. It has been clinically proven to help patients with prostate cancer undergoing radiation therapy reduce urinary, sexual, and gastrointestinal adverse effects while improving their quality of life. The SpaceOAR Hydrogel is intended to assist in limiting the amount of radiation given to the rectum during prostate cancer therapy. Radiation therapy for prostate cancer patients aims to kill cancer cells without harming the healthy tissue around them. The SpaceOAR Hydrogel (SOH), a polyethylene glycol-based substance injected transperineally between the prostate and the rectum to increase the space between the organs, is one such product [41].

3.10. Traceit® Hydrogel Tissue Markers

PEG hydrogels are suitable as fiducial markers since they are well-tolerated and have low immunogenicity, such as the TraceIT Tissue Marker. The iodine contrast material is impregnated in the hydrogel microbeads. It has only been used for marking purposes in areas such as bladder, gynaecologic, and oesophageal abnormalities, mainly the tumor. The marking is stable and visible in Magnetic Resonance Imaging, computed tomography, and ultrasound for a period of 3 months. It gets cleared completely out of the body in a span of 7 months of implantation by the renal filtration system. An absorbable tissue marker with a three-month lifespan is the polymer known as TraceIT Tissue Marker. It is mostly composed of water and iodinated cross-linked PEG. The glass pre-filled syringe, the plastic receiving syringe, the sterilised Luer-Luer connector, and the needle made up the TraceIT Tissue Marker. Prior to use, the PEG hydrogel was mixed. A plastic receiving syringe was filled with an injectable PEG hydrogel after being mixed five times between the two syringes [42].

3.11. Coaptite®

A suspension of spherical calcium hydroxylapatite (CaHA) particles in an aqueous-based gel makes up Coaptite, an injectable, sterile, non-pyrogenic implant. The gel carrier comprises sodium carboxymethylcellulose, sterile water for injection, and glycerin. At the bladder neck, coaptite is injected submucosally. The bladder, neck, and urethra gain increased tissue mass and soft tissue augmentation due to the Coaptite injection. Coaptite is recommended for treating Stress Urinary Incontinence (SUI) caused by an Intrinsic Sphincteric Deficit (ISD) in adult females. The action method is to thicken the soft tissue around the urethra, which causes a coaptation and increases urethral resistance to pee loss. For the urethral tissue, the CaHA particles serve as a space-filling bulk [43].

3.12. Bulkamid® Hydrogel

Women with stress urinary incontinence brought on by weak urethral sphincter muscles can be treated with bulk amid a thick, long-lasting gel. The Bulkamid Urethral Bulking System is a single-use kit made up of sterile syringes containing the Bulkamid gel, a rotatable sheath, and injection needles. Weak urethral sphincter muscles, which open and shut the tube from the bladder that drains pee from the body, are one factor in stress urinary incontinence (urethra). When exercising or making other movements like sneezing or coughing, adult women with stress urinary incontinence who may also experience uncontrollable urination may benefit from using Bulkamid. It is injected close to the bladder in the urethra's wall. Bulkamid increases the size of the urethral wall after being injected into the body, helping to strengthen the urethra and improve control over urine flow. Water and cross-linked polyacrylamide make up the bulk of hydrogel, provided sterile in 1 mL pre-filled syringes [44, 45].

4. Results

4.1. Some of the Injectable Hydrogels under different Phases of Clinical Trials

4.1.1. Biosentry®

The BioSentry tract sealant system is a device that seals the pleural space during a pleural puncture by injecting a self-expanding hydrogel plug into the pleural space after a lung biopsy. The injected hydrogel plug creates an airtight seal that encloses the pleural puncture and provides accurate marking of the biopsy location for surgery, which is done later. Usage of BioSentry tract sealant shows a significant 80% reduction in chest tube placements and reduced an average of 83% per cent of time spent by patients after surgery for recovery [46, 47]. Table 2 provides information on the few injectable hydrogels that are currently under different phases of clinical trials.

4.1.2. Promgel-OA

Osteochondral tissue engineering is a promising methodology for curing early Osteoarthritis (OA), chondral lesions, and people with progressive joint pain. This procedure has been improved by introducing injectable hydrogels for tissue repair; these hydrogels have a wide range of properties, such as their porous framework and high-water content, and they are similar in properties to the natural Extracellular Matrix (ECM), ability to provide a suitable environment for cellular differentiation and the ability to hold the cells within the matrix [48]. The hydrogels are also easy to deliver to the target place; they can repair geometrically complex abnormal defects, which have been a critical game-changer for their success in tissue repair. Osteoarthritis is the most common disorder due to aging, resulting in pain and immobility in joints. Although surgery can reduce pain with a significant amount of money and morbidity, Injectable hydrogel (Hyaluronic acid) is a more efficient and long-term solution for knee and joint issues [49].

4.1.3. Hyadd®

Hyaluronic acid (HA) is a hydrogel with a high molecular weight glycosaminoglycan. Hyaluronic

Table 2. Some of the injectable hydrogels are under different phases of clinical trials

Clinical trial registry number/ Status	Study type	(Company/ University name)/ Collaborator	Name/Material	Injection type	Applications
NCT02224924 Phase III Active, not recruiting	Interventional	Memorial Sloan Kettering Cancer Center	Polyethylene glycol	Visceral pleura	Reduction of pneumothorax during lung biopsy procedures
NCT03307564/ Active, Recruiting	Interventional	Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins /Augmenix, Inc.	Absorbable Radiopaque Tissue Marker/ Polyethylene glycol	Percutaneous	Marker interface between the duodenum and pancreas for imaging pancreatic adenocarcinoma
NCT03125226/ Completed	Interventional	Fred Hutch/University of Washington Cancer Consortium	Polyethylene glycol	Percutaneous	Tissue marker for bladder carcinoma
NCT04061733/ Recruiting	Interventional	Promedon	PROMGEL-OA Hydroxyethyl cellulose	Knee	Treatment of knee pain caused by symptomatic osteoarthritis
NCT02187549Unknown	Interventional	Fidia Farmaceutici S.p.A.	HYADD® 4 hydrogel/ Non-crosslinked hyaluronic acid alkylamide	Intra-articular	Ease pain caused by knee osteoarthritis
NCT04045431 / Active, Not Recruiting	Interventional	Contura	PAAG-OA/ Polyacrylamide	Intra-articular	Knee osteoarthritis
NCT03897686 / Unknown	Interventional	Research Centre BIOFORM	NOLTREX™, II-III grade OA/ Polyacrylamide hydrogel with silver ions	Intra-articular	Knee osteoarthritis
NCT03067090 / Unknown	Interventional	A2 Reumatologi Og Idrætsmedicin	Aquamid Reconstruction (AR)/ Polyacrylamide	Intra-articular	Knee osteoarthritis
NCT02763956 / Recruiting	Interventional	Dr Med. Paolo Maino Viceprimario Anestesiologia	GelStix® Nucleus	Intra-discal	Treatment of chronic discogenic low back Pain
NCT04115345 / Recruiting	Interventional	inRegen	Renal autologous cell therapy (REACT)/ Gelatin and renal cells	Renal cortex	Treatment of chronic kidney disease caused by congenital anomalies of the kidney and urinary tract

Source: <https://clinicaltrials.gov/>

acid is both elastic and viscous; these properties are determined by the concentration and ratios in which they are injected. Arthritis patients suffer from a low elasto-viscosity of the synovial fluid, and hyaluronic acid with higher molecular mass with high elasto-viscosity is used as a substitute for the synovial fluid in the joints. HYADD shows a better effect on synovial pathological changes in arthritis patients, as it primarily consists of water; there is much less

chance of rejection by the body. HYADD also decreases synovial intimal hyperplasia with very few injections [50-52].

4.1.4. Paag-OA

Polyacrylamide gel is injected via Intra-Articular (IA) for people with symptoms of osteoarthritis. PAAG consists of 2.5% polyacrylamide and 97.5%

non-pyrogenic water. It has a unique molecular structure that allows the movement/exchange of water with its surrounding tissue without deforming from its original structure. PAAG is also bio-compatible, non-biodegradable, non-absorbable, and structurally stable. It has also been used for urinary incontinence and soft tissue augmentation [53, 54].

4.1.5. Noltrex®

Knee Osteoarthritis is a chronic, progressive degenerative disease that deteriorates the knee joint's cartilage. Polyacrylamide hydrogels are used for treating Knee Osteoarthritis via intra-articular injection to reduce the pain and increase the longevity of the joint. They are biocompatible, biostable, synthetic polymers with silver ions that are used as replacements for synovial fluids. They contain 4% polyacrylamide and 96.9% distilled water, with 0.01 to 0.02% silver ions. The various side effects, such as hematoma, gel deposition, tissue reactions including infection, transient surgical side pain, inflammation, tenderness, foreign body granuloma, gel migration, asymmetry, irregularity, and induration, were reported very rarely [55, 56].

4.1.6. Aquamid®

Aquamid is one of the new generations of injectable tissue fillers, which are exclusively used for aesthetic facial correction and reconstruction. The Aquamid gel contains 97.5% sterile water and 2.5% polyacrylamide, which makes it viscous and elastic. It is completely biocompatible, eternal, and does not migrate from the site of injection. Aquamid Reconstruction (AR) is a type of polyacrylamide hydrogel, which is a biocompatible, non-toxic, visco-elastic synthetic gel, highly durable, has good tissue compatibility, and is well tolerated by the mammalian tissues, in turn, provides in-vivo vessel and growth of fibers. AR takes effect by integrating with the soft tissues over time, by combining molecular water exchange and vessel ingrowth. When injected via intra-articular injection, AR results in permanent pain relief, improving the joint's padding or cushioning effect [57, 58].

4.1.7. Gelstix®

Gelstix is a hydrolyzed polyacrylonitrile (hydrogel) used to treat lower back pain. The injection of hydrogels in the nucleus pulposus gives us an effective regenerative intradiscal therapy. The hydrogel plays an important role as a reservoir of hydration, increasing pressure and improving the pH balance, leading to the preservation of the spinal discs. Gelstix reduces the intensity of the pain 6 months post-surgery compared to other treatments and surgeries [59].

4.1.8. React

The biological ingredients for the REACT are acquired from the percutaneous tissue patient's kidney cortex. The kidney cells/tissue then undergoes a selection process that gives Selected Renal Cells (SRC) for renal repair, and also the cells can be frozen and stored for future use in liquid nitrogen. Before being reinjected inside the patient, they undergo treatment with thermolabile gelatin hydrogel and are then injected into the patient's renal cortex. The MR imaging of the kidneys guides the volume injection of the SRC. Cells in the targeted area/Cortex region. The patient will need to return to the hospital for ongoing clinical evaluations and assessments following this surgery. After that, each patient serves as their own control and must attend twice a year to take two dosages [60].

5. Conclusion

Injectable hydrogels hold great potential in numerous biomedical applications, including wound healing, tissue engineering, drug delivery, and regenerative medicine. Injectable hydrogels offer multiple benefits, which include minimally invasive delivery, targeted drug administration, and the capacity to conform to the shape of the tissue or wound site. Previous studies have demonstrated significant potential for a number of synthetic and natural polymers that are currently being explored as injectable hydrogels in different stages of clinical trials. Among the products that have been approved for clinical use are hydrogel-based treatments for osteoarthritis and postoperative pain management. Despite the promising results of preclinical studies, additional clinical data are needed to assess the safety,

efficacy, and long-term effects of injectable hydrogels. Optimizing injectable hydrogel composition, distribution, and dosing is necessary to improve patient outcomes and minimize side effects. Injectable hydrogels have the potential to significantly improve patient care and completely transform the biomedical applications sector. With much more research and development, injecting hydrogels may become a standard part of the therapeutic environment for a range of health problems.

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