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"Design And Development Of Fresh Water Fish Scalp Derived Collagen/CMC Based Hydrogel For Treating Diabetic Foot Ulcer"

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ABSTRACT *As a useful food ingredient and food enhancer, collagen is highly prized. Usually, enzymes, microbes, and acid or alkali treatments are used to extract it. Collagen is extracted from the scale of tilapia fish. The yield of protein extraction was 2-3 times higher in extruded size samples. Compared to scale samples that were not extruded. Collagens are analysed using molecular weight distribution, FTIR, and a particle size analyser. If neglected, diabetic foot ulcers (DFU), a common and frequently incapacitating consequence of diabetes, can lead to lower limb amputations. Three-dimensional networks of hydrophilic polymers, known as hydrogel dressings, have been demonstrated to have outstanding fluid handling capabilities, low toxicity, and great biocompatibility. They can also absorb and hold huge amounts of water. Additionally, by facilitating angiogenesis, migration, and cell proliferation, hydrogels produce a moist wound environment that accelerates wound healing. As a result, hydrogels have shown promise as wound coverings to aid with DFU healing. During Preparation of Hydrogel we had prepared Solution A. Ca-Cs Solution (Collagen Solution+ Citric Acid),1-3% of Collagen and 0.4-0.6% of Citric Acid. Solution B. CMC solution 1-3% Of CMC (Carboxymethyl Cellulose), Solution C. PVA solution 0.5-1% of PVA (Polyvinyl Alcohol), Solution D. nZnO+ Glycerol. Mixing of solution makes (CMC+PVA) Solution and CMC/PVA+ Ca-Cs Solution. Film and Thick layer hydrogel was prepared and analysed by using FTIR, SEM AND TEM.*

Key Points: *-Collagen, Diabetic Foot Ulcer, Hydrogel, Freeze Throw Method, Acid soluble Collagen.*

INTRODUCTION

Three-dimensional cross-linked networks of hydrophilic polymers with high water absorption capacity are known as hydrogels. Because the polymeric backbone contains hydrophilic pendant groups like -CONH, -OH, -COOH, -CONH2, -SO3H, etc., they have the ability to retain water. They also preserve their three-dimensional structure when swollen through chemical or physical crosslinking. Covalent connections will exist between the polymer chains in chemically crosslinked hydrogels, while physical forces including hydrophobicity, hydrogen bonding, ionic interactions, and chain entanglements support physically crosslinked hydrogels (Sharma D 2022). When Wichterle and Lim created crosslinked poly (hydroxyethyl methacrylate) (pHEMA) in 1960, hydrogel was first used for biological purposes. For biological applications, the first synthetic hydrogels of HEMA were created using EGDMA (ethylene glycol dimethyl acrylate) as a cross-linker. These were then utilized to make contact lenses (Maitra J.2014).

Hydrogels' special qualities that promote wound healing make them extremely promising materials for the treatment of DFU. Hydrogels' mode of action for treating DFU is influenced by a number of variables. First of all, hydrogels' high water content contributes to the preservation of a moist wound environment, which is necessary for the best possible wound healing. In turn, the hydrogel's water content promotes the flow of nutrients and oxygen between the surrounding tissues and the wound bed, establishing an environment that is essential for tissue repair, cellular metabolism, and the healing process that follows (Ko A, Liao C. 2023).

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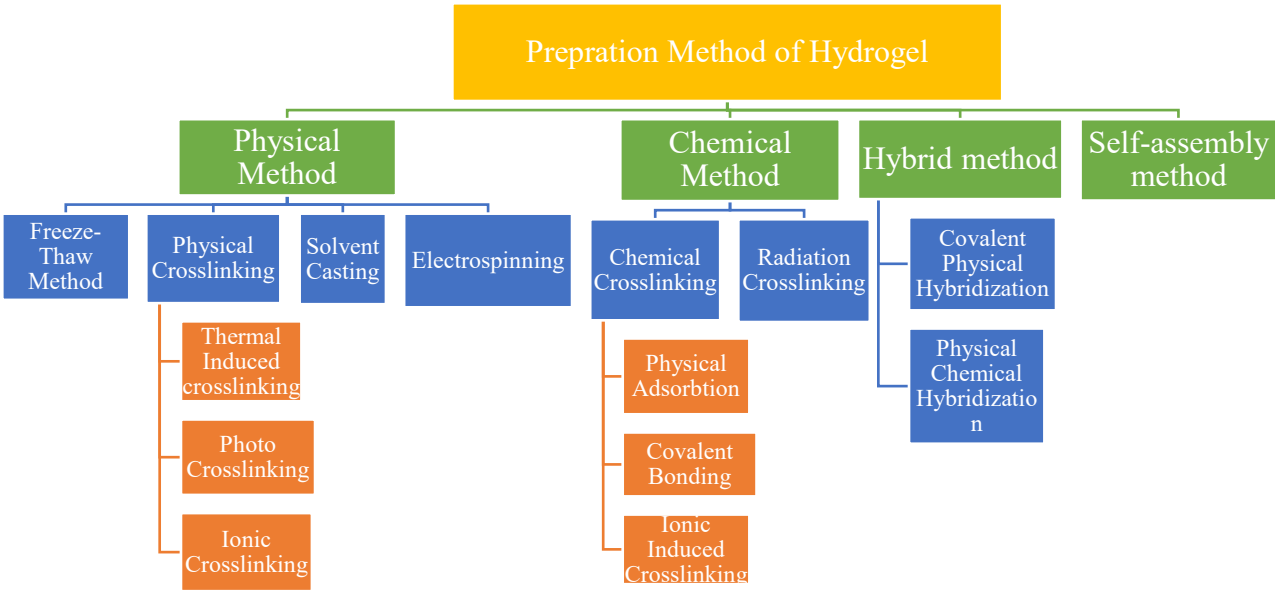
Nowadays, biocompatible hydrogels are employed in bone regeneration, cartilage wound healing, wound dressing, and as drug delivery vehicles. hydrogels are frequently advantageous for fostering angiogenesis, cell migration, quick nutrient transport, and high water content. Collagen is one type of naturally occurring hydrogel-forming polymer (Ko A, Liao C. 2023). The therapeutic impact of hydrogels made from natural polymers like collagen, alginate, or chitosan in the context of diabetic wound healing has been extensively studied in recent years. Collagen has been thoroughly investigated for use in the production of biomaterials due to its diverse biological activity, mechanical qualities, and biodegradability (thermal or enzymatic). Collagen, in particular, has been shown to have a beneficial effect on wound healing in wound care applications by promoting tissue regeneration through growth factor release and structural support (Güiza-Argüello VR.2022).
Hydrogels can now be toughened using a variety of techniques, enabling load-bearing applications. Slip-link networks, nanocomposite hydrogels, double network hydrogels, multifunctional crosslinked hydrogels, homogeneous hydrogels, hybrid ionic-covalent IPN hydrogels, and others are among the techniques for creating tough hydrogels. It has been demonstrated that each of these techniques increases hydrogel strength, and several considerably increase hydrogel toughness (Naficy S. 2013).

DIFFERENT PREPARATION METHOD OF HYDROGELS:



1. PHYSICAL METHOD

I. freeze-thaw method

The physical process of repeatedly freezing and thawing a polymer solution is known as "freeze-thaw preparation," and it is used to prepare hydrogels. The preparation of the polymer solution, freezing of the solution, and thawing of the frozen solution are the three main phases involved in the freeze-thaw method. By varying the number of freeze-thaw cycles, the freeze-thaw approach enables the creation of hydrogels with regulated characteristics, including mechanical strength and swelling behavior(Ko A, 2023).The hydrogel production process in F-T occurs in two stages: the precursor solution freezes at 0 °C and then thaws at room temperature. The primary goal is to regulate the freezing and thawing processes of ice

crystallization and ordered structure development, respectively, to give the hydrogels the best possible qualities.Without the use of chemical covalent bonding agents, the freeze-thaw method approach is essentially a physical crosslinking technique. Hydrogen bonds, electrostatic systems, or hydrophobic forces between polymer chains can all be used to create physical hydrogels.The freeze-thaw method technique, which examined the super-molecular structure of PVA-based hydrogels, was initially presented by Peppas in 1975. The F-T technique was gaining popularity by that point. Willcox (1999) examined the microstructure of PVA hydrogels using the freeze-thaw method method. The freeze-thaw method method's hydrogels' crystallinity characteristics have also been thoroughly explained. Hydrogels can be created using natural polymers, like polysaccharides, rather than synthetic ones by employing the freeze-thaw method technique (Waresindo WX. 2023).

They discovered that PVA chains may be broken up and the molecular weight of the polymer increased at the same time by the freeze-thaw process. Furthermore, the formation of water crystals in the gels during the freeze-thaw cycle may cause a shearing action in the polymer solution, which could split polymer chains and produce free radicals as a result. Additionally, these free radicals have the potential to combine with other chains, producing high molecular weight material and chemical crosslinks. According to this hypothesis, the gelation that occurred during the freeze-thaw process was brought on by chemical interactions, as demonstrated by the findings of TGA and XRD analyses (Hong KH. 2010).

Crosslinking Methods	Material and Crosslinking agent	Crosslinking Temperature and Time	Highlight and Challenges	Applications and References
freeze-thaw method	Aloevera, PVA, and GO are crosslinking agents.	The temperature was frozen for 20 hours at -15°C and thawed for 4 hours at 5°C. repeated three times.	The hydrogel was made without the use of a crosslinking agent, and it had mechanical qualities similar to those of skin tissue, great hydrophilicity, vitality up to 295%, and the ability to reduce bacteria up to 99.94%	Burn Wound Dressing(Waresindo WX. 2023).
freeze-thaw method	GLE/PVA	The freezing temperature at -25°C for 20 hours, and the thawing temperature at 24°C for 4 hours for 6 cycles.	It was noticed that the porous hydrogel's morphology grew larger as the GLE portion was added. It has a 207% swelling capacity, making it a promising material for wound dressings.indicates that as the GLE concentration is raised, the hydrogel's degree of crystallinity decreases.	Dressing wounds (Waresindo WX.2021)

freeze-thaw method	Hemicelluloses, PVA, and chitin	Thaw at RT for 1 hour after 10 hours of freezing at -20°C. Cycles 0, 1, 3, 5, 7, and 9 were repeated.	A stiffer structure, more stable thermal characteristics, and a higher degree of crystallinity were the outcomes of the increased number of F–T cycles. On the other hand, a lamellar structure developed during three F–T cycles, resulting in a drop in the hydrogel equilibrium's swelling.	Thermal Stability and Compressive Strength (ratio Guan Y.2014)
freeze-thaw method	PVA (polyvinyl alcohol) with ws-chitosan (water soluble chitosan)	Freezing and thawing were repeated up to three times to form hydrogels.	Because of their low mechanical strength, irradiation-only hydrogels are not suitable for use as wound dressings. According to SEM data, the initial processing step primarily determines the final structure of hydrogels created by combining irradiation and freeze-thawing.	dressing a wound (Yang X.2008).

Table 1.How hydrogel properties are affected by the settings used in the Freeze-thaw method of hydrogel synthesis.

II. PHYSICAL CROSSLINKING METHOD

a) Thermal Induced Crosslinking

Heating the hydrogel solution over the glass transition temperature or polymer melting point causes thermally induced crosslinking. The heat increases the mobility of the polymer chains, allowing them to interact with one another in non-covalent ways. A crosslinked hydrogel is produced when the temperature is decreased, immobilizing the polymer chains (Ko A, 2023).An automatic temperature control attachment on a UV-2550 spectrophotometer was used to measure the thermo-response of the hydrogels and polymer.By examining how the photoluminescence (PL) spectra changed with heating and chilling, the light emission properties of the hydrogel and polymer were also described. To identify the phase transition, PL spectra were gathered at different temperatures (Hou f.2019).

There are two types of thermosensitive hydrogels: one exhibits a phase change from insoluble to soluble in water at the upper critical solution temperature (UCST), while the other experiences a reverse phase transition at the lower critical solution temperature (LCST) (Xia M,2015). The LCST gelation behaviour of MC solution was impacted by the polymer and salt concentrations . For example, when 0.1 M CaCl2 and 0.1 M Na2HPO4 were added to the MC solution, the gelation temperature reduced from 32.0 °C to 29.1 °C, the corresponding gelation duration dropped from 54 s to 14 s. The process of creating the UCST (upper critical solution temperature) induced hydrogel involves chilling a polymer solution to a temperature known as UCST.Because the hydrophobic micelle cores become water soluble, hydrogels are formed by micelle aggregation below UCST and disintegrate when the temperature returns to UCST.(Hu

W. 2019). A minimally invasive injection of the precursor aqueous solutions into the body, followed by in situ hydrogel production triggered by physiological temperature, is made possible by the special thermo-induced sol–gel phase transitions. Polypeptide hydrogels are intriguing prospects for a variety of biomedical applications because of these benefits (Zhao D.2023). Thermal gelation can create protein-based hydrogels, and chemical crosslinkers like glutaraldehyde can improve their mechanical characteristics (Maitra J.2014).

b) **Photo Crosslinking**

One interesting technique for the creation of hydrogels is the photo-crosslinking reaction using light irradiation. One interesting technique for creating hydrogels is the photo-crosslinking reaction when exposed to light. Following application of the hydrogels to the wound, light is produced by exposing the wound to certain visible or ultraviolet light, which initiates polymerization. The hydrogels then solidify in place and undergo a transformation from liquid to solid. Hydrogels with a stable three-dimensional structure, high stiffness, and strength can be produced by this chemical crosslinking process using photoinitiated unsaturated double-bond polymerization. The standard properties of "light control" are present in this type of photo-crosslinking hydrogel: Nonphysical touch and space-time controllability allow them to be produced in situ at the desired time and location, better suit the wound, and remain unaffected by physical variables like pH and temperature. Additionally, damp wounds can be better fitted by the solidification of fluids. Both engineering and medicine have used the photo-crosslinking technique, including in tissue engineering and the creation of biomaterials for drug delivery(Ma H.2022).

Photo-crosslinkable hydrogels have garnered significant interest in tissue engineering applications in recent years because of their extracellular matrix (ECM)-like structure and good biocompatibility. By exposing a photosensitive system made up of photo-crosslinkable hydrogels, photo-initiators, and other substances like cells and medicinal chemicals to ultraviolet or visible light, they can be readily biofabricated(Wang Y. 2021).Compared to traditional physical or chemical crosslinking techniques, photocrosslinking offers numerous benefits. The benefits include minimum heat production, quick crosslinking rates (a few seconds to a few minutes) at room temperature, and control over both space and time throughout the polymerization process.4. Many researchers have used costly high-intensity light sources, including the OmniCure Series 2000 (Excelitas Technologies, Waltham, USA), with wavelengths ranging from 100 to 400 nm ultraviolet (UV) spectrum, to accomplish the quick photocrosslinking of hydrogels (Wang Z. 2016).

c) Ionic Crosslinking

Polyelectrolyte complexes are created when oppositely charged macromolecules interact with one another through electrostatic interactions.Chitosan is a naturally occurring polycationic biopolymer made up of 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-dglucopyranose linked by β-bonds. Therefore, by electrostatic interactions between its cationic amino groups and anionic groups from other natural anionic polyelectrolytes, including pectin, chondroitin sulfate, and alginate, chitosan readily forms polyelectrolyte complexes (PECs) (Hu W. 2019).Using ionic crosslinking agents, like calcium ions, to join the polymer chains in the hydrogel network is known as "ionically induced crosslinking." Alginate hydrogels are frequently prepared using this technique, and they can be crosslinked by adding a calcium ion solution (Moura MJ.2011).

III. SOLVENT CASTING METHOD

SCPLs (Solvent Casting Particulate Leaching Method) require less difficulties and are simple to process. A SCPL was created in order to address the shortcomings of the fiber bonding method. This method involved casting the sieved salt particles into a glass container after dispersing them in a PLLA/chloroform solution. In chloroform, the salt particles were insoluble. After allowing the solvent to drain, any remaining material was vacuum-dried (Prasad A 2017). Because of its relaxed and reasonably priced

process, the solvent casting method is a dependable, preferred, and widely utilized casting technique out of all the ones that are offered. In the solvent casting method, a polymer and plasticizer are dissolved, the solution is spread out on a substrate, and the solvent is removed. This results in the intercalation of plasticizer molecules and the molecular orientation of the polymer chains, which forms a film. This process involves dissolving the polymer(s) and plasticizer(s) in a volatile solvent, such as ethanol, acetone, water, or a mixture of solvents. If a medication is added, it can be dissolved or suspended in the mixture, then poured into a mold and allowed to dry (Borbolla-Jiménez FV 2023).

Crosslinking Methods	Material and Crosslinking agent	Characterisation and Drug Used	Highlight and Challenges	Applications and References
Solvent Casting method	Heat-crosslinked silver nanoparticles with polyvinyl alcohol (PVA).	Inductively coupled plasma (ICP) analysis was used to quantify the amount of silver released.	Blended PVA cast films eliminate the requirement for high temperature crosslinking and provide better control over hydrogel dissolution and silver release. Silver release profiles and membrane dissolving control are further enhanced using blended PVA electrospun membranes. These blended PVA membranes and films provide better, more affordable methods for producing hydrogel wound dressings that are long-lasting and anti-infective.	wounds and burns (Jackson J. 2021).
Solvent Casting method	films of graphene oxide (GO) sheets and silk fibroin (SF) with layered structures	An ESCALAB 250XI photoelectron spectrometer (ThermoFisher Scientific, USA) was used for XPS. On an AR-G2 rheometer (TA Instruments, USA), rheological investigations were carried out.	In conclusion, the aqueous dispersion was mechanically blended to successfully create stable SF–GO hybrid hydrogels for the first time.	biomedical uses, including tissue engineering and biological scaffolding (Huang L. 2013).
Solvent Casting method	Chitosan, glutaraldehyde	5-Fluorouracil using differential scanning calorimetry (DSC) and infrared spectroscopy	5-FU molecules' diffusivity through the chitosan membrane decreased as a result of more 5-FU molecules being trapped in the CGN system's chitosan membrane than in the C-N system.	(Yang JM. 2011).

Solvent Casting method	PVA's hydroxyl group is esterified with gelatin's carboxyl group.	FTIR spectroscopy was performed on gelatin, PVA, and the hydrogel membrane between 4000 and 400 cm−1. The investigation made use of an FTIR spectrophotometer (NEXUS-870, Thermo Nicolet Corporation, Waltham, MD).	It was discovered that the hydrogel was superabsorbent, hemocompatible with human blood, and capable of facilitating SA diffusion.	biomedical uses, including moist wound dressings and medication delivery methods (Pal K.2007).

IV. ELECTROSPINNING METHOD

The ability to produce nanofibers in large quantities using needleless electrospinning holds enormous promise for nanofiber research and development. It is still very difficult to figure out how to enhance electrospinning efficiency in order to produce high-quality nanofibers. Researchers have concentrated on needleless electrospinning as a way to increase the manufacturing rate of nanofibers via electrospinning. However, because of unstable whipping or inadequate solvent evaporation, the fiber quality from needleless electrospinning might not be as high as that from needle electrospinning (Hosseini 2022).

A new method was created and tested to get over the current drawbacks of conventional electrospinning procedures. Instead of using electrical forces like in electrospinning, this novel technique, called Forcespinning, uses centrifugal forces. A series of spinnerets that were created to overcome the technological difficulty of reducing the fibers down to the nanoscale scale enable a revolutionary production system when paired with the speed, collecting, and heating that has been stabilised forcespinning can be used with both melted and solution materials. The financial (solvent recovery step) and environmental (material contamination) effects of toxic polymer solvents are removed by the capacity to melt the materials in the spinneret (Sarkar K 2010).

2.CHEMICAL METHODS

I) Chemical Crosslinking

Chemical cross-linking can be caused by tiny molecules, UV light, cationic/anionic condensation, or free radicals. The amount of crosslinker, reaction duration, temperature, stirring speed, and an initiator/catalyst (type and concentration) all affect the degree of crosslinking in free-radical, condensation, and small-molecule crosslinking. The degree of cross-linking in UV light is regulated by the radiation dose from high-energy ionizing radiation, gamma, or x-rays. Because physical cross-linking is created by secondary pressures, it is weaker than chemical cross-linking. Chemical cross-linking is far more resilient to mechanical, thermal, and other forces. The chemical (covalent) cross-linking of the polymer, conventional polymerization methods including condensation and free-radical polymerization are frequently employed. Depending on the link formation, the free-radical and condensation polymerization techniques provide either a degradable or non-degradable polymer. While polymers produced by physical cross-linking may cause interference during application due to weak cross-linking by secondary forces, polymers acquired by these approaches may not cause any issues during application because of robust cross-linking by primary forces. Chemical cross-linking is therefore frequently chosen (Mane 2015).

a) Physical Adsorption

Dye wastewater is being treated using a variety of physical, chemical, and biological techniques. Adsorption, chemical catalytic degradation, liquid membrane separation, electrolysis, biological treatments, oxidation, and other processes have all been used to study different removal techniques. The efficacy, expenses, and environmental effects of these procedures differ, though. Because they are readily available, less expensive, and have a greater range of applications, the physical adsorption process and chemical catalytic degradation are far more competitive than other techniques. Finding adsorbents that satisfy the norms and requirements of the water treatment sector while also being affordable, highly effective, environmentally friendly, and available in bulk amounts is crucial (Chen 2020).An effective technique to eliminate hazardous heavy metal ions from water bodies has been called for by researchers. Because the adsorption approach is simple to use on a wide scale and exhibits encouraging results for the removal of heavy metal ions, it can be used in real-world applications. Many adsorbents have been created and documented, however hydrogels stand out due to their ease of handling, preparation, and reusability. In order to create hydrogels, polymers are often cross-linked to produce a three-dimensional structure with high porosity and high functionality (Perumal 2021).

b) Covalent Bonding Method

With the quick advancement of polymer science and life science fields in recent decades, hydrogels based on dynamic covalent bonding (DCB) have garnered a lot of interest and investigation. The materials used to create DCB hydrogel skeletons are sourced from a greater variety of sources, DCB hydrogel design strategies are more developed, and DCB introduction methodologies are more adaptable and manageable. The DCB hydrogels differ from conventional ones in a number of special ways, such as their capacity for self-healing and their reactivity to certain environmental stimuli. These characteristics make DCB hydrogels one of the smart materials with the most potential for use in the biomedical field, despite the fact that there are still certain obstacles to overcome. The construction of the dynamic chemical bond is crucial for creating DCB hydrogels. The imine bond, acylhydrazone bond, disulfide, boronate ester bond, and Diels-Alder (D-A) reaction are among the common dynamic chemical bonds and reactions that serve as the foundation for DCB hydrogels (Ye J 2020).

c) Ionic Induced Method

The use of ionically crosslinked alginate hydrogels in tissue engineering has been extensively researched. Alginates are frequently crosslinked via ionic contact between the carboxyl groups and multivalent anions like Ca2+ and Fe3+. Alginates have been used with various synthetic polymers to combine the best features of both worlds in more intricate hydrogel designs, such as double network hydrogels and interpenetrating network hydrogels. Numerous studies have examined the impact of various ions on the characteristics of double network poly(acrylamide)/alginate hydrogels and single network alginate hydrogels (Xin 2023).

Crosslinking Methods	Crosslinking agent and Characterization	Highlight and Challenges	References
Ionic Induced Method	examined using X-ray diffraction, DSC, DTG, and FTIR.	The chitosan hydrogel membrane's water content was affected by the addition of sodium alginate and the development of ionic crosslinks. Non-freezing water and freezing water were seen in both uncrosslinked and ionically crosslinked chitosan membranes, although in varying quantities.	(Ostrowska-Czubenko 2009).

Ionic Induced Method	FTIR Spectroscopy, Chitosan's protonated amino groups and crosslinking agents' anionic functional groups	Ionically crosslinked chitosan membranes are created when low and/or high molecular crosslinking agents are added to chitosan membranes. The creation of ionic crosslinks between the protonated amino groups of chitosan and the anionic functional groups of crosslinking agents is demonstrated by FTIR spectroscopy.	(Pieróg 2009).
Ionic Induced Method	poly(ethylene glycol) (PEG) with poly(L-glutamic acid) (PLG),	By crosslinking poly(ethylene glycol) (PEG) with poly(L-glutamic acid) (PLG), a new polypeptide hydrogel has been created. It was demonstrated that the PLG-PEG hydrogel was extremely hydrophilic, and that the degree of swelling increased with increasing PLG ionization and varied with pH. In addition to electrostatic phenomena like internal ion osmotic pressure and ion–ion repulsion,	biodegradable hydrogels that respond to pH (Markland 1999).

RADIATION CROSSLINKING

It is commonly known that ionizing radiation is a very practical tool for modifying polymer materials via grafting, degradation, and crosslinking processes. Numerous items, such as foams and car tires made by radiation crosslinking, use these changed materials (Nagasawa N 2004). These days, it is typical practice to modify biodegradable plastics using high-energy radiation (either an electron beam or a gamma beam). The general goal of radiation therapy for polymers is to introduce a specific quantity of chain scission, which lowers the molecular weight of the polymer, or crosslinking, which increases the molecular weight of the polymer. Tensile strength, elongation, modulus of elasticity, hardness, and softening temperature will all rise as a result of crosslinking. However, chain scission reduces these characteristics. Therefore, drug delivery systems, wound dressings, injectable polymers, implants, contact lenses, and stimuli-responsive devices are the primary application areas for hydrogel materials made with high energy irradiation. High-energy irradiation offers a hygienic and effective way to create gels, but it can also cause polymer chains to break down and lose their viscosity. Under ionizing radiation, polysaccharides, particularly cellulose derivatives, often break down by breaking glycosidic bonds. However, in certain situations, high-energy radiation can be used to create chemical gels in mild conditions that resemble paste and do not break down polysaccharides (Pekel N 2004).

HYBRID METHOD

By allowing for the modification of microscale hydrogel characteristics (suitable for cell adhesion, migration, and proliferation) as well as the incorporation and customization of drug or gene delivery features (suitable for microenvironment-sensitive and targeted therapy), hybrid hydrogels open up new possibilities in biomedical applications. Along with the creation of biodevices, biosensors, and contact lenses, they have been used as therapeutic interventions in a number of illnesses, such as wound healing, osteogenesis, malignancies, myocardial infarction, Parkinson's disease, and infections (Palmese 2019).

COVALENT-PHYSICAL CROSSLINK

Crosslinking Methods	Material and Crosslinking agent	Highlight and Challenges	Applications and References
Ionic and covalent cross-linking	Glycerolphosphate chitosan	It was demonstrated that the hydrogel-based compositions were harmless. When a co-cross-linking formulation was injected in vivo, the gel quickly formed and localized to the injection site, where it stayed for at least a week.	thermosensitive character (Moura MJ.2011).
Reaction of photocrosslinking and Diels-Alder (DA) produced by heat	Injectable hydrogel based on hyaluronic acid (HA)	According to every findings, the injectable hydrogel created by the photo-crosslinking reaction and the thermally induced DA reaction has a good chance of being used in cartilage tissue engineering because of its steadily improving mechanical capabilities.	Tissue engineering (Wang G.2018)
Ionic and covalent cross-linking	In the presence of alginate (Alg), networks of covalently crosslinked polyacrylamide (PAAm) or poly(acrylic acid) (PAA) were created.	Each end of this hydrogel was made to be harder, tougher, and pH-insensitive in order to act as a tendon-like substance that would secure the gel muscle to its mechanical supports. The central portion of the hydrogel was intended to be a pH-triggered artificial muscle.	Applications in biomedicine and actuators (Naficy S. 2013).
chemical and physical	50% (wt.%) glutaraldehyde (GA) aqueous solution with analytical-grade genipin powder (GEN)	The structural metrics, elongation ratio, thermal characteristics, and crystallinity of the hybrid hydrogels crosslinked with genipin were comparable to those crosslinked with glutaraldehyde. Nevertheless, it was discovered that the two hybrid hydrogels' elastic moduli differed somewhat.	the food, agricultural, environmental, tissue engineering, and regenerative medicine sectors(Garnica 2016).

DIFFERENT DISORDERS TREATED WITH HYDROGELS

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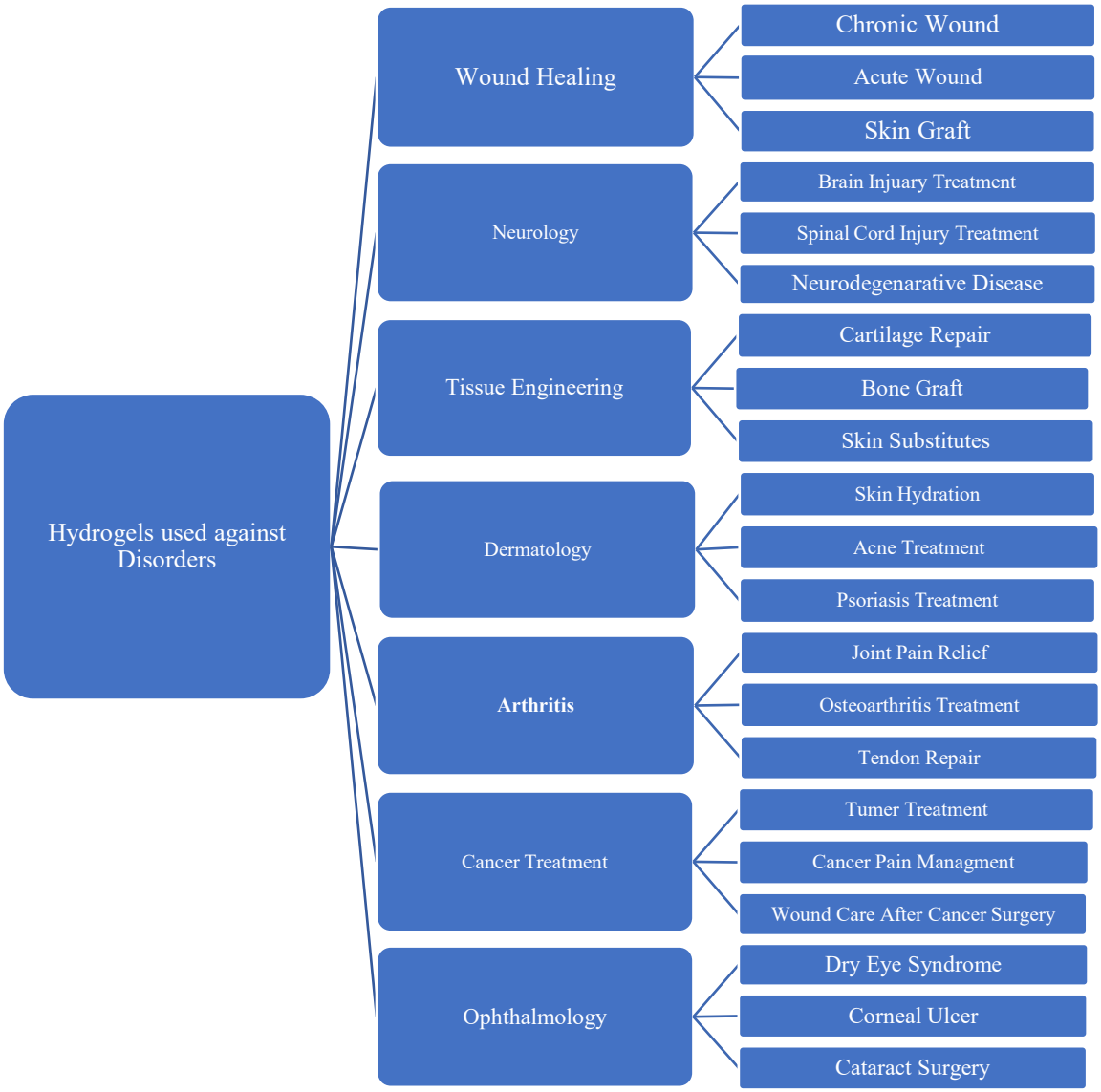

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Table :- List of Clinical Trials on Diabetic Foot Ulcer hydrogel/ Wound Healing.

NCT Number/ Study Complitance	Study Title	Brief Summary	Interventions	Sponsor

NCT06584617/05/09/2024	The Purpose of This Study is to Assess Clinical Efficacy and Safety of Berovenal¬Æ Intended to Promote Treatment and to Expedite Chronic Diabetic Foot Ulcer Healing	The goal of this clinical investigation is to evaluate clinical efficacy of medical device Berovenal¬Æ intended to promote treatment and to expedite healing of chronic diabetic foot ulcer in male or female subjects aged 18-85 years with diabetes mellitus (type 1 or 2) and with present diabetic foot ulcer by providing moist environment similar to intracellular environment of the damaged tissue. It will also learn about the safety of medical device. Participants: * Use medical device Berovenal¬Æ or a reference device every day for 8 weeks or to the time point when the diabetic foot is closed * Visit the clinic once every 2 weeks for checkups and tests * Keep a diary of their symptoms and the number of times they use medical device Berovenal¬Æ or a reference device	DEVICE: Berovenal¬Æ | DEVICE: NU-GEL Hydrogel with Alginate	VULM s.r.o.
NCT04497805/01/06/2024	Clinical Study of ALLO-ASC-SHEET in Subjects With Diabetic Wagner Grade II Foot Ulcers	This is a phase 2 double-blind clinical study to evaluate the efficacy and Safety of ALLO-ASC-SHEET in subjects with Diabetic Wagner Grade II Foot Ulcers, compared to placebo therapy.	BIOLOGICAL: ALLO-ASC-SHEET	Anterogen Co., Ltd.
NCT05607979/01/05/2024	Restoring Tissue and Evaluating Novel Treatments for Efficacy in Wounds	This is an IRB-approved multicenterstudy.This non-inferiority study aims to evaluate differential healing rates between Lavior Diabetic Wound Gel and other Hydrogels. Study therapy will be started in the outpatient setting and followed accordingly.	DRUG: Lavior Diabetic Wound Gel | DRUG: Smith & Nephew Solosite Gel Hydrogel Wound Dressing	Lavior Pharma Inc.
NCT03754465/23/10/2023	Clinical Study of ALLO-ASC-SHEET in Subjects with Diabetic Foot Ulcers	This is a phase 2 double-blind clinical study to evaluate the efficacy and Safety of ALLO-ASC-SHEET in subjects with Diabetic Foot Ulcers, compared to placebo therapy.	BIOLOGICAL: ALLO-ASC-DFU | PROCEDURE: Hydrogel SHEET(Vehicle control)	Anterogen Co., Ltd.

NCT0566 1474/12/1 2/2022	Fitostimoline¬Æ Hydrogel Versus Saline Gauze Dressing in Diabetic Foot Ulcers	management, and treatment of DFUs are represented by health education, strict control of blood glucose and cardiovascular risk factors, offloading, local debridement, and adequate dressing. A wide variety of dressing is available, and these include basic contact dressings (low adherence dressings such as saline gauze, paraffin gauze or simple absorbent dressings) and advanced dressings (alginate, hydrogel, films, hydrocolloid, form). in a monocentric, two-arm, open-label, randomized, controlled trial.	DRUG: Fitostimoline ¬Æ hydrogel group|DRU G: Saline gauze group	Federico II University
NCT0362 4023/09/0 7/2021	TWB-103 for Treating Lower Limb Ulcers on Patients With DM	Primary Objective :To assess the safety profile of TWB-103 administered to subjects with diabetic lower limb ulcers Secondary Objective: To explore the efficacy of TWB-103 administered to subjects with diabetic lower limb ulcers	DRUG: TWB-103	Transwell Biotech Co., Ltd.
NCT0337 0874/02/0 2/2020	Clinical Study to Evaluate Efficacy and Safety of ALLO-ASC-DFU in Patients With Diabetic Foot Ulcers.	This is a phase III double-blind study to evaluate the efficacy and safety of ALLO-ASC-DFU in patients with Diabetic Foot Ulcer, compared to placebo therapy.	BIOLOGIC AL: ALLO-ASC-DFU|PROC EDURE: Vehicle sheet	Anterogen Co., Ltd.
NCT0263 1512/30/0 4/2019	Evaluation of Woulgan in Diabetic Foot Ulcer	The aim of the current study is to support the performance and safety of Woulgan¬Æ in the treatment of diabetic foot ulcer in comparison with the commercially available hydrogel Intrasite. Healing and untoward medical events to be evaluated.	DEVICE: WoulganGel |DEVICE: Intrasite Hydrogel	Biotec Pharmacon ASA
NCT0236 1931/12/0 6/2018	Topical Erythropoietin Hydrogel Formulation for Diabetic Foot Ulcers	RMD-G1 is indicated for treating DFUs in adult patients with diabetes mellitus and aims to accelerate the healing of diabetic foot ulcers. RMD-G1 is an adjunct treatment, and not a substitute for good diabetic wound care, which includes initial debridement, wound cleansing, pressure relief, and infection control. In this trial, RMD-G1 is applied daily onto a clean wound at 0.25g per sq. cm. wound surface. After its application, the wound will be covered with a dressing in order to prevent leakage of the hydrogel and contamination of the wound area.	DRUG: A hydrogel containing erythropoieti n|DRUG: Hydrogel (as a part of SOC)	Remedor Biomed Ltd

NCT0370 0580/15/1 0/2016	Clinical Trial Using the Proteolytic Fraction P1G10 From V. Cundinamarcensis to Heal Diabetic Foot Ulcer	The aim of the study was to investigate the role of the proteolytic fraction from Vasconcelleacundinamarcensis, designated as P1G10, on healing of chronic foot ulcers in neuropathic patients diagnosed with diabetes type 2. Fifty patients were enrolled in a prospective, randomized, double-blind trial, to verify the efÔ¨Åcacy and safety of a topical dressing containing 0.1% P1G10, versus a Hydrogel (positive control) protocol currently applied at the Health Center to treat this condition.	DRUG: Hydrogel treatment|DRUG: P1G10	Carlos E Salas
NCT0142 7569/Aug ust 2015	Efficacy Study of IZN-6D4 Gel for the Treatment of Diabetic Foot Ulcers	The purpose of this study is to determine if topical application of a hydrogel that contains plant extracts will improve healing of diabetic foot ulcers when compared to treatment with a hydrogel alone.	DRUG: IZN-6D4 Gel|OTHER: Placebo hydrogel	Izun Pharma Ltd
NCT0220 9662/01/1 2/2015	Safety and Efficacy Study of APIC-PRP in Non-healing Diabetic Foot Ulcers	Patients have a diabetic foot ulcer that is older than 4 weeks and has been treated with physician-selected standard of care treatment such as debridement, hydrogel or saline irrigation, primary dressing, and offloading will be randomized into one of two groups, the Standard of Care (SoC) or APIC-PRP + SoC. APIC-PRP has high level of platelets that produce growth factors that can help in wound healing.	DEVICE: APIC-PRP|OTHER: Placebo, Saline plus standard of care	Cytonics Corporatio n
NCT0114 3727/01/1 0/2012	Enzymatic Versus (vs) Autolytic Debridement of Diabetic Foot Ulcers	This study compares two standard methods for cleaning the surface of wounds on the feet of patients with diabetes mellitus. The question being asked is whether inflammation of the wound affects the ability of one or both of the methods to work.	DRUG: Santyl|DRUG: Tegaderm Hydrogel	Healthpoin t
NCT0097 1048/01/0 1/2011	Evaluation of the Effects of HP828-101 Versus Standard of Care in the Management of Partial or Full Thickness Wounds	To compare HP828-101 to standard of care for the management of partial or full thickness wounds	DEVICE: HP828-101|DEVICE: Hydrogel/Hydrocolloid	Healthpoin t
NCT0044 6472/01/0 9/2010	Evaluation of Windowed Casts With and Without Regranex¬Æ Gel for Healing Diabetic Neuropathic Ulcers	The objective of this study is to compare the effectiveness and safety of windowed casts with Regranex¬Æ (topical becaplermin gel) versus placebo (inactive medication) for treatment of diabetic ulcers on the legs and feet.	DRUG: Regranex¬Æ|DRUG: Hydrogel	Southern California Institute for Research and Education

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