International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 43-53 www.ijprajournal.com ISSN: 2456-4494

A Comprehensive Review on Collagen Peptide-Based Nanocomposite Hydrogels for Wound Healing

Abirami.A, Grace Rathnam*
Dept. of Pharmaceutics, C.L.Baid Metha College of Pharmacy, Thoraipakkam, Chennai-600097

Date of Submission: 01-05-2025 Date of Acceptance: 10-05-2025

ABSTRACT: Collagen-based hydrogels have gained significant attention as biomaterials for wound healing, tissue engineering, and drug delivery due to their biocompatibility, biodegradability, and ability to mimic the extracellular matrix (ECM). Efforts have been made to improve these hydrogels' mechanical strength, stability, and bioactivity through crosslinking techniques and the incorporation of nanomaterials and peptides. These enhancements have shown potential in improving bioactivity, antimicrobial resistance, and osteogenic properties, making them suitable for tissue regeneration and controlled drug release. Nanomaterials such as hydroxyapatite, graphene oxide, and chitosan contribute to the enhanced functionality of collagen hydrogels. However, challenges remain in addressing issues of biocompatibility, scalability of manufacturing, and clinical implementation. Despite these obstacles, collagen peptide-based nanocomposite hydrogels offer promising solutions for various biomedical applications, particularly in regenerative medicine, Wound healing, and tissue engineering.

KEYWORDS: Collagen peptide, Nanocomposite hydrogel, extracellular matrix, regenerative medicine, Wound healing

I.INTRODUCTION

Academic interest in collagen peptide hydrogels for biomedical applications has increased because they align with biological requirements and the extracellular matrix (ECM) by being nonreactive to living tissue, degradable, and structurally similar to native tissue. The hydrogel environment remains highly hydrated for supporting cell growth along with differentiation processes and tissue engineering work. The commercially available collagen hydrogels degrade rapidly at the same time they fail to provide adequate mechanical stability needed for cellular attachment and tissue regenerative processes[1-3].Researchers solved these issues through the creation of nanocomposite hydrogels which combine collagen peptides with strengthening biomaterials such as polysaccharides cellulose nanocrystals (CNCs) together with bioactive nanoparticles [4,5].The mechanical properties of hydrogel networks receive enhancement through nanocomposite structures because they create robust polymer interlocking configurations that minimize enzymatic damage.

Scientific investigations have used crosslinking methods to develop collagen hydrogels that retain stability and get stronger mechanically. The hydrogel network obtains reinforcement through the implementation of enzymatic crosslinking via transglutaminase and chemical crosslinking methods with genipin or glutaraldehyde as well as physical crosslinking via ionic bonding mechanisms or UV irradiation. Hydrogels become more durable for biological applications because modification techniques provide both sustained drug management systems and cell encapsulation mechanisms for regenerative medicine usage.The scientific evidence shows that collagen peptides in nanocomposite hydrogels demonstrate great potential for wound healing and cartilage repair as well as drug delivery capabilities [6].

1. Collagen

The human body contains collagen protein at the top position for abundance with 30% of protein composition therefore making it essential for connective tissue structure. The protein exists mainly in the fundamental body tissues which include skin, bones, tendons and ligaments and cartilage and blood vessels and extracellular matrix. The amino acids glycine and hydroxyproline together with proline form the building blocks of collagen as it takes shape in its three-helix protein structure. The collagen triple-helix structure adopts stability from hydrogen bonds which leads to high tensile strength and flexibility in connective tissues so they can resist mechanical forces and stay structurally intact.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 43-53 www.ijprajournal.com ISSN: 2456-4494

Specialized cells from mesenchymal tissue produce collagen through the activity of fibroblasts in skin and connective tissue and osteoblasts in bones as well as chondroblasts working in cartilage tissue. Fibroblasts and osteoblasts and chondroblasts generate procollagen from which enzymes create hydroxylated and glycosylated collagen fibrils. Tissue repair and cohesion become possible through the process where fibrils cross-link to create durable fibers. The tissue adhesive properties of collagen extend beyond supportive functions because it directs cellular healing responses together with tissue regeneration mechanisms and cell binding activities and engages with signaling factors as well as receptors to affect diverse biological activities

The natural regulation of collagen synthesis and breakdown operates across lifespan yet aging together with UV radiation exposure and smoking and pollution factors and selected medical issues generate collagen breakdown and consequently cause wrinkles and joint stiffness and damage to connective tissues. Recent biomedical applications make extensive use of collagen because this biomolecule exhibits compatibility with biological tissue and natural breakdown properties. The essential structural function of this biomolecule positions it as an essential molecule [7].

1.1 Properties of Collagen

Collagen stands out through its remarkable mechanical features that make the structural protein essential for human body health. The strong tensile capabilities of collagen ensure that mechanical stress does not cause damage to tissue structures because it resists stretching forces. The triple-helix arrangement offers collagen its exceptional strength because it interweaves three α-chains while hydrogen bonds secure the construction. The extensive cross-linking in collagen fibers strengthens their material stability because it enhances their ability to resist deformation forces. The method in which collagen arranges itself depends on tissue requirements since tendons display parallel fiber alignment for resisting persistent tensile pull forces yet skin contains a network pattern which yields elasticity and flexibility. The woven arrangement of collagen fibers in cartilage serves shock absorption whereas bone structures use them to endure load-bearing forces. Collagen structures adapt through distinct fibers in various tissues which facilitate important biomechanical stability as well as the proper functioning of all tissues

Among at least 28 collagen types present in the human body Type I, II, and III represent the most widespread forms. Skin as well as tendons ligaments and bones consist mostly of the abundant form of collagen known as Type I. The main function of Type II collagen in the body occurs through its presence within cartilage tissue to enable flexible joints with shock-absorbing capabilities. Blood vessels together with skin and internal organs obtain vascular integrity and wound healing through Type III collagen. Medical applications combine with cosmetic and pharmaceutical uses of collagen because of its versatile biological properties. Medical practitioners extensively utilize collagen in wound dressings and tissue engineering together with reconstructive surgeries because it enhances cell sticking along with tissue regeneration and healing processes.The suitable biological interaction properties and tissue regeneration properties of collagen make it an essential biomaterial for medical and industrial applications [8,9].

2.Peptide

A peptide chain consists of linked amino acids through peptide bonds produced by combining the amino acid carboxyl group with the amino acid amino group and generating water as a byproduct. Peptides differ from proteins through their shorter amino acid content since they contain fewer than 50 amino acids and exist as linear structures or cyclic shapes or branched arrangements. Natural and synthetic methods equally exist for generating peptides since they can occur in living biological systems and scientists can also synthesize them. The biological processes within living organisms benefit from peptides which serve as hormones, neurotransmitters, growth factors and immune system regulators and enzymes. Insulin together with oxytocin and glucagon represent important hormonal peptides for regulating metabolism and maintaining reproductive abilities as well as homeostasis. Peptides act as cellular communication signals that control immune response together with various biological processes which span from inflammation to tissue repair to wound healing. AMPs represent vital host defense components because they exhibit antimicrobial (bacteria) and antifungal and antiviral protective abilities. Peptide function and specificity are mostly governed by the amino acid sequence and structural prompts of peptides since modest

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 43-53 www.ijprajournal.com ISSN: 2456-4494

sequence alterations cause substantial functional modifications. Peptides serve multiple functions in pharmaceuticals and biotechnology and therapeutic care mostly through their applications in targeting drug delivery systems and vaccine creation and diagnostic diagnostic devices.

2.1 Properties of Peptides

The chemical sequence and amino acid components found in peptides determine unique characteristics that emerge. Hydrophilicity and hydrophobicity exist as essential features of peptides. Certain peptides dissolve in water but others demonstrate lipid membrane preference instead of water solution. The solubility property stands important for peptides that act as signal molecules or antimicrobial elements since membrane interaction depends on their solubility. Peptides have the ability to take up different secondary structures including alpha-helices along with beta-sheets and randomly shaped coils. The function of dynamics depends on how a peptide adopts its three-dimensional structure. Various hormones and neurotransmitter peptides obtain specific structural arrangements that support strong binding to target cell receptors. The stability of peptides functions as a crucial element because they demonstrate sensitivity to environmental elements which include temperature as well as pH and ionic strength. The biological activity of peptides exists as a distinctive and special property. Insulin serves as one of the widely recognized peptides because it controls blood sugar levels and other peptides known as antimicrobial peptides (AMPs) function as antibiotics. Research shows that many peptides serve as therapeutic agents for pain relief solutions alongside hormone replacement programs while treating cancer and diabetes conditions.

3. Methods of Isolation of Peptides from Collagen

3.1. Enzymatic Digestion

The enzymatic digestion technique represents a standard method for obtaining peptides from collagen through its extraction process. Scientific enzymes collagenase and pepsin perform the specific task of breaking collagen into peptide fragments through enzymatic processes.

3.1.1. Collagenase Digestion

The triple-helix structure of collagen can be broken down by collagenase enzyme into peptide fragments through enzymatic cleavage. This approach is specifically used because collagenase enzyme activates selectively against collagen molecules instead of disturbing different protein types during procedures [10].

3.1.2. Pepsin Digestion

Pepsin performs protease activity as an acidic protease to break down collagen molecules during acidic digestion procedures (pH 1-2). Pepsin split the collagen polypeptide chain into several peptide fragments. The isolation of peptides from acidic conditions such as skin or cartilage works best with pepsin treatment.

Advantages

High specificity for collagen
Peptide fragments retain biological activity
The structure of the peptide stays intact when researchers use mild solution conditions.

Disadvantages

The significant drawback includes both the expense of enzyme solutions and the need for conditioning the reaction parameters.
The selection of an enzyme for digestion could result in non-specific cleaving of the material.

3.2. Acid Hydrolysis

The method of acid hydrolysis decomposes collagen through the application of hydrochloric acid (HCl) to produce amino acids and shorter peptide sequences. Acid hydrolysis serves as an ideal technique to achieve a comprehensive breakdown of collagen when necessary. Collagen treatment by concentrated hydrochloric acid at 110°C maintains temperatures for 24 hours splits apart peptide bonds to obtain peptides and amino acids as products. Fluorescent-labeled hydroxylamine is one method to purify the peptides by using liquid chromatography (LC) or centrifugal filtration. Following acid hydrolysis the mixture needs neutralization before recovering the peptides through liquid chromatography (LC) or centrifugal filtration methods.

Advantages

This method effectively produces chain fragments from collagen molecules.
This procedure works efficiently for processing big collagen amount quantities.

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 43-53 www.ijprajournal.com ISSN: 2456-4494

Disadvantages
Pleasant conditions should be maintained during peptide analysis because severe circumstances tend to damage fragile peptides.
The method needs post-hydrolysis procedures to remove the separated peptides.

3.3. Mechanical Disruption (Hydrolysis)

The decomposition of collagen fiber structures takes place through three mechanical processes which include grinding sonication along with high-pressure homogenization. Three mechanical processes divide collagen structures which produces protein structure breakdown that releases peptides. The production of fine collagen powder by grinding methods creates more surface area for improved triple-helix breakdown. The sonication waves break collagen structures apart which leads to production of microscopic collagen peptides from degraded protein. Better outcome results from combining this approach with acid hydrolysis or enzymaticdigestion. Through shear forces application in High-pressure Homogenization the collagen material breaks down into particles and peptides.

Advantages
Fast and relatively simple
No need for enzymes or chemicals

Disadvantages
Less control over the peptide size
Potential for mechanical damage to the peptides
Often requires subsequent purification steps.

3.4. Solvent Extraction

The extraction method based on solvents utilizes organic solutions such as urea and guanidine hydrochloride for dissolving collagen materials to obtain peptides. Heat along with agitation treatment helps scientists extract peptides from collagen structures by breaking down the molecular arrangement of the collagen material. During the procedure collagen absorbs a solvent such as urea solution to achieve collagen dissolution. Following the peptide extraction from the supernatant solution you can proceed with additional techniques such as precipitation or chromatography for processing.

Advantages
A large amount of collagen material can be exposed to the processing method.
Gentle on peptide structures

Disadvantages
Requires careful solvent removal
The effective use of this technique can be restricted by toxic effects of solvents.

3.5. Peptide Synthesis (Ex Vivo) and Recombinant Methods

Scientists have developed two synthesis techniques for creating collagen peptides either through recombinant DNA technology or chemical synthesis. The methods produce synthetic versions of collagen-based peptides instead of extracting peptides directly from collagen. The expression of specific collagen gene-derived peptide sequences takes place in microorganisms along with eukaryotic cells through recombinant DNA technology. The cells produce the specific peptides after which they become suitable for purification[11]. The reaction sequence of amino acids for collagen-like peptide synthesis follows solid-phase peptide synthesis (SPPS) protocols .

Advantages
High purity and controlled peptide sequences
Users can customize standardized products through an existing process to satisfy different application requirements.

Disadvantages
Requires specialized equipment and expertise
The process often fails to duplicate entire natural collagen peptides during specific situations [12].

4.Applications of Peptides

The biological activities and functionalities of peptides as short chains from amino acids bring great value to numerous applications across different fields.

4.1 Application of Peptides in Wound Healing

The healing process relies on peptides as bioactive agents that control biological mechanisms of inflammation together with cell growth and tissue reconstruction and collagen structure formation. The biological sequence leading to wound healing after injuries and surgical interventions receives enhancement from peptides that possess active properties. The wound healing process receives stimulation through growth factor peptides that make fibroblasts and keratinocytes migrate toward the wound site for tissue regeneration. Recovery of tissue occurs when Peptides called Platelet-Derived Growth Factor

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 43-53 www.ijprajournal.com ISSN: 2456-4494

(PDGF) and Epidermal Growth Factor (EGF) naturally stimulate two mechanisms wherein new blood vessel formation (angiogenesis) combines with cell multiplication and enhanced collagen production [13]. The therapeutic application of these peptides involves their topical administration or their addition to dressings which helps speed up the process of wound healing and tissue regeneration specifically for non-healing or chronic wounds.

Apart from promoting cell migration and collagen synthesis peptides demonstrate antimicrobial capabilities. The antimicrobial peptides (AMPs) with defensins and cathelicidins act as natural antibiotics within the innate immune system to prevent infections at the wound area. Antimicrobial peptides incorporated into wound care remedies establish a healing-friendly condition since they support tissue restoration and fight infections simultaneously.

Numerous advantages of using peptides to treat wounds stem from theircapacity to boost cellular activities alongside anti-inflammatory capabilities and infection defense together with enhancement of collagen formation. Advanced wound dressings as well as creams and gels integrate bioactive molecules of natural origin or synthetic production for superior wound treatment compared to traditional methods. The implementation of peptides enhances healing speed and results in tissues with better quality which produces stronger reinforced skin after healing completes[14].

5.Hydrogels

A hydrogel is a three-dimensional structure made up of chains of hydrophilic polymers networks holding, swelling, and absorbing large volumes of aqueous fluids. These materials are made of networks of natural or synthetic polymers and have a high degree of absorbency. Additionally, due to their high water content, these materials have a remarkable level of flexibility that is comparable to that of real tissue. Because of its flexible nature, biocompatibility, and versatility in manufacturing, hydrogel has emerged as one of the most promising materials in the biomedical industry. The physical characteristics of hydrogels are similar to those of the physiological tissue environment, which enables them to fulfil a range of clinical requirements, including medication and cell delivery, tissue engineering scaffolding, and immune regulation[15,16].

5.1 Structure of Hydrogel

Crosslinked polymeric chains form a network structure that makes up hydrogels' solid forms. Hydrogels are capable of exhibiting unlimited molecular weight due to their 3D network-like topologies. The molecular weight of the polymer chain between the cross-links and the mesh size determine the hydrogel shapes at the molecular level. In general, cross-linked hydrogels were created using both chemical and physical crosslinking techniques, which are based on entanglement or hydrogen bonding[17].

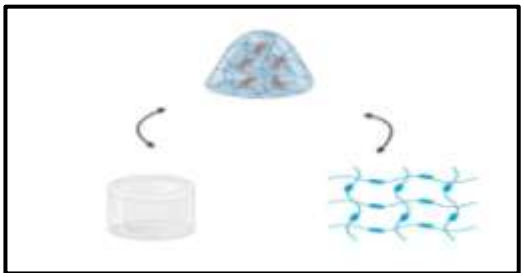

Fig. 1. Structure of Hydrogel

5.2 Classification of Hydrogel:

Hydrogels are classified according to their source, composition, ionic charge, crosslinking, properties, configuration, and environmental stimulation. Polymer chains are crosslinked to form hydrogels. Hydrogels come from a variety of sources, including natural, synthetic, and semi-synthetic polymers. Hydrogels can be classified as natural, synthetic, or semi-gel depending on the polymer source. Depending on their composition, the hydrogels' polymers can be homopolymers, copolymers, semi-interpenetrating networks (semi-IPNs), or IPN hydrogels. Depending on their structure, hydrogels can be crystalline, semi-crystalline, or amorphous.The hydrogels can be categorized as chemical or physical hydrogels based on the crosslinking technique. Permanent connections in chemical hydrogels are made of end-functionalized macromeres that have undergone polymerization and covalent crosslinking. Physical crosslinking include Ionic interactions, hydrogen bonds, and crystallization that make up the transitory junction of physical hydrogels.Chemical hydrogels are made up of end-functionalized macromeres of polymer chains that are polymerized and covalently crosslinked to form permanent connections. Nonionic, anionic, cationic, and ampholytic hydrogels are the four categories into which they can be separated according to the ionic charge. Aside from nonionic hydrogels, the other hydrogels are pH-sensitive

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 43-53 www.ijprajournal.com ISSN: 2456-4494

because of their ionic groups and have electric charges in their polymer chains. Hydrogels can react chemically or physically. Physical and chemical factors have been shown to modify the physical characteristics of hydrogels, including self-assembly and deformation (a change from a swelling to a shrunken hydrogel). These stimuli can be found in external settings or solvents. Physical stimuli include Temperature, pressure, light, electric fields, and magnetic fields. Chemical stimuli include molecular species, solvent composition, pH, and ionic strength [18,19].

6.Fabrication method of Hydrogels

Different fabrication methods serve hydrogels depending on their kind and intended function as well as their necessary properties. The main methods include:

6.1. Physical Crosslinking (Non-Covalent Interactions)

Physical crosslinking techniques dominate hydrogel fabrication because they work without chemical crosslinkers which enables them to remain biocompatible enough for biomedical uses. Hydrogel network stability through physical crosslinking methods depends on various non-covalent connections including ionic bonds and hydrogen bonds and hydrophobic forces and crystallization events. Programs based on ionic gelation serve as a common method to create networks in polyelectrolyte hydrogels through opposite polyelectrolyte interactions. The tissue engineering drug delivery tool alginate hydrogels can transform into a gel structure through exposing them to divalent cations such as calcium (Ca^{2+}) or barium (Ba^{2+}) ions[20].The process of chitosan-based hydrogel formation occurs through tripolyphosphate (TPP) crosslinkers that produce stable hydrogel matrices with demonstrated excellent biocompatibility[21].Such hydrogels benefit from gentle crosslinking procedures that safeguard biological functions of either cells or drugs or proteins encapsulated within them. Narrowing down potential biomedical applications becomes difficult due to their poor mechanical properties along with fast deterioration that occurs in physiological solutions.Certain polymers undergo thermo-responsive gelation through which they convert from solution to gel form as temperatures change. Poly(N-isopropylacrylamide) (PNIPAAm) represents a commonly researched polymer which stays dissolved in water below 32°C LCST but creates a hydrogel network above that temperature because of hydrophobic bond formation .PNIPAAm-based hydrogel formulations show prime applications in tissue engineering scaffolds as well as drug delivery systems because these systems form hydrogels in situ through body temperature-based responses. Self-assembly-based hydrogel formation significantly relies on the function of hydrophobic interactions. Pluronic® (poloxamers) among other amphiphilic block copolymers create micelles during heating before transitioning into gels for sustained drug delivery methods. The process of crystallization-induced gelation occurs when polymers separate into different phases and crystallize like PVA cryogels that develop through multiple freeze-thaw processes. The PVA-based hydrogels achieve their strength enhancement and elastic properties through this particular technique for making them applicable in artificial cartilage work and biomedical implants as well as wound dressing uses. Throughout the manufacturing industry hydrogel suppliers emphasize composite formulation development for physically crosslinked hydrogels because this method creates biocompatible easy-to-prepare devices which have lower mechanical strength than chemically crosslinked hydrogels[22].

6.2. Chemical Crosslinking (Covalent Bonding) in Hydrogel Fabrication

Hydrogels produced using chemical crosslinking methods become durable and strong because stable covalent bonds form between neighbouring polymer chains. The drug delivery applications along with tissue engineering and wound healing process benefit from durable chemical crosslinked networks through covalent bond formation. Free radical polymerization stands as the main chemical crosslinking approach which uses acrylamide, polyethylene glycol diacrylate (PEGDA), or methacrylatedgelatin as monomers while free radical initiators assist in their polymerization process. The hydrogel matrix achieves its highly crosslinked state as radicals that initiate chain formation originate from ammonium persulfate (APS) and tetramethylethylenediamine (TEMED). The free radical polymerization process leads to advantageous results because it produces simple systems which are easily controlled while allowing hydrogels to acquire modifiable properties through changes in monomer concentration and reaction duration. The presence of unreacted free radicals can cause cytotoxic reactions thus biomedical applications need further purification

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 43-53 www.ijprajournal.com ISSN: 2456-4494

methods to eliminate their impact. A different method of covalently crosslinking hydrogels exists through the enzymatic action of horseradish peroxidase (HRP) which catalyzes the formation of hydrogel networks. A crosslinking process mediated by HRP uses H_2O_2 together with phenolic compounds to create permanent covalent connections within biomaterials made from gelatin and silk fibroin and hyaluronic acid. Enzymatic crosslinking presents advantages through its biological compatibility and physiologically suitable reaction processes which enable its use inside tissues for medical purposes [23-25].

The particular and efficient bioorthogonal features of thiol-ene click chemistry-based crosslinking applications have stimulated growing academic interest. Hydrogels from thiol-ene reactions occur through -SH group bonding with -C=C- groups to form stable networks that promote minimal side effects while maintaining strong biocompatibility. The hydrogel technology primarily serves biofabrication, functionalized scaffolding and injectable gels applications because click chemistry enables exact architectural control of hydrogels while maintaining gentle reaction conditions. Aldehyde-based crosslinking represents another vital covalent method that uses Schiff base reactions between aldehydes (-CHO) and amines ($-NH_2$) to create imine bonds. The crosslinking method has become standard practice for creating hydrogel networks based on biopolymers through the interaction of oxidized polysaccharide aldehyde groups with protein amine groups in systems like oxidized alginate linked to gelatin. Hydrogels based on Schiff base chemistry demonstrate good application in tissue engineering and drug delivery systems because their reversible crosslinks enable adjustable breakdown times alongside self-healing ability. Controlling the reaction conditions properly remains essential for aldehyde-based crosslinking because improper management can produce unwanted degradation along with excessive crosslinkage that affects both elasticity and biocompatibility of the hydrogel. Researchers have identified specific chemical crosslinking techniques for biomedical and industrial applications[26,27].

7.Applications of Hydrogels:

Hydrogels have been used in various fields of biomedical applications .

7.1 Hydrogel for Wound dressing:

Hydrogels have been a future solution to wound healing because they can provide a moist environment, are capable of exudate absorption, and are shape-responsive. Chronic wounds and acute wounds are a huge economic burden to global health because of delayed healing, infection, and cost-effectiveness. Conventional dressings cause pain on removal, which sticks to the wound. They do not possess healing functions. Conversely, hydrogels, particularly those derived from natural and synthetic polymers, are efficient in inducing tissue regeneration an(d the delivery of therapeutic agents [28].

Diniz et.al[29] prepared hydrogels from natural polymers such as sodium alginate and gelatin, with the addition of silver nanoparticles (AgNPs) for antimicrobial properties. AgNPs prepared at different concentrations (1.0, 2.0, and 4.0 mM) exhibited UV–Vis peaks between 430–450 nm, which is characteristic of spheroidal shapes, further supported by TEM. FT–IR spectral analysis indicated predominant intermolecular bonding, while in vivo trials in rats were found to demonstrate improved wound healing, wound contraction, and increase in granulation tissue. Such AgNP-loaded hydrogels exhibited extensive antibacterial action toward Pseudomonas aeruginosa and Staphylococcus aureus, having minimum inhibitory concentrations (MIC values) in picomoles, and lack of cytotoxic effects on fibroblasts. Overall, advanced hydrogel systems are capable of performing multiple functions such as antibacterial properties, biocompatibility, adhesion to tissues, and accelerated healing, which makes them ideal candidates for clinical wound care therapies [30].

8. Fabrication Techniques for Nanocomposite Hydrogels

The development of nanocomposite hydrogels for improved external stimulus sensitivity and biological activity through fabrication methods blending, grafting, in situ precipitation and swelling has been achieved [31,32].

8.1 Blending Method

Among the easiest approaches to create nanocomposite hydrogels stands the blending method. A mixture of hydrogel precursors and various nanoparticles including iron oxide, silver, gold, graphene oxide or hydroxyapatite takes place before gelation happens. The blending method works well because it utilizes basic mixing procedures that allow the incorporation of bioactive nanoparticles while maintaining their operational

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 43-53 www.ijprajournal.com ISSN: 2456-4494

capabilities. Silver nanoparticles combined with collagen hydrogels show antimicrobial effects because of their blend with collagen hydrogels yet iron oxide nanoparticles enable targeted drug delivery and hyperthermic response through their magnetic characteristics.

8.2 Grafting and Functionalization

Hydrogel polymers undergo functional group and nanoparticle covalent bonding to their backbone structure through the grafting process. The mechanical properties of hydrogel matrices become stronger through this technique while it also preserves nanomaterial stability and prevents phase separation. Cells adhering and proliferating better alongside differentiating more efficiently occurs when hydrogels receive bioactive ligands or peptides or drugs through functionalization thereby rendering this technique beneficial for tissue engineering applications. Hydrogel properties receive precise control from graft polymerization which uses radiation or enzyme or chemical catalyst-initiated processes [33].

8.3 In Situ Precipitation

The method of in situ precipitation provides exceptional performance for distributing nanoparticles evenly within hydrogels. The synthesis of nanoparticles occurs inside hydrogel networks while polymerization takes place thus maintaining even particle dispersion and stopping separation phenomena. The nanoparticle dispersion obtained through this method results in improved mechanical strength and bioactivity for hydrogels. Hydrogels obtain improved osteoconductivity and mineralization properties from hydroxyapatite and calcium phosphate nanoparticles through in situ precipitation techniques that also prevent nanoparticle aggregation.

8.4 Swelling and Porogen Leaching

Hydrogels swell through solvent or water intake into their matrix before porogen leaching leads to porous structures. The technique serves as an effective method to produce hydrogels that require connected porosity for cell penetration and nutrient movement and blood vessel formation in tissue engineering applications. The use of nanomaterials during the swelling process delivers better mechanical abilities and functional qualities for hydrogel structures.

8.5 3D Printing and Biofabrication

Biomimetic structures can be developed at high resolution through 3D printing procedures during nanocomposite hydrogel fabrication to obtain accurate spatial hydrogel composition . 3D-printed nanocomposite hydrogels gain better mechanical properties together with bioactivity and stimulus-sensitive capabilities when they absorb nanomaterials including graphene oxide, bioactive glass and magnetic nanoparticles.

8.6 Smart and Stimuli-Responsive Nanocomposite Hydrogels

Nanocomposite hydrogels activated by external stimuli including pH, temperature, light and magnetic fields have become highly important for biomedical applications [34].

Hydrogels that are pH-responsive change their swelling action according to pH fluctuations to fulfill drug delivery requirements for acidic tumour sites as well as gastric systems.

Hydrogels which contain poly(N-isopropylacrylamide) (PNIPAM) components undergo temperature-dependent phase changes for the purpose of controlled drug release and tissue bonding.

Sliding stiffness properties in nanocomposite hydrogels become accessible through exposure to UV or NIR light for exact temporal as well as spatial control of material stiffness and degradation.

Hydrogel properties become remotely adjustable through magnetic fields after adding iron oxide nanoparticles thus making them appropriate for targeted drug delivery and soft robotic applications.

9.Biomedical Applications of Collagen Peptide Nanocomposite Hydrogels

The biomedical use of collagen peptide-based nanocomposite hydrogels demonstrates versatility due to their application in wound healing processes.

9.1 Wound Healing Applications

Scientists created collagen peptide-based nanocomposite hydrogels for wound healing acceleration through the improvement of mechanical characteristics alongside better gelation properties and biological features. Researchers have discovered that drug combinations of recombinant human collagen-peptide (RHC) with chitosan hydrogels create excellent outcomes for wound healing through their stimulatory effects on fibroblast proliferation and collagen synthesis and

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 43-53 www.ijprajournal.com ISSN: 2456-4494

blood vessel formation. Scientists studied these hydrogels through burn wound model tests which proved their ability to improve tissue healing and re-epithelialization processes.

Antimicrobial effects together with electrical conductivity become possible with conductive nanocomposite hydrogels containing methacrylatedgelatin (GelMA) and Ti_3C_2 (MXene) in combination with collagen-binding antimicrobial peptides (V-Os). Hydrogels with conductive properties serve chronic wound healing purposes because they enable electrical signal channels that drive keratinocyte motility while creating new epithelium.

Biocompatible hydrogels with included biological agents epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) accelerate tissue regeneration along with inducing blood vessel creation (angioesis). The biofunctionalized hydrogels establish an ideal condition for tissue recovery through their mechanism of controlled inflammation management and improved cell movement and bactericidal properties.

The development of antimicrobial peptide-infused collagen hydrogels constitutes an approach to manage multidrug-resistant bacterial infections during wound treatment. Chronic wound care benefits from hydrogel systems that maintain specific antimicrobial properties which stop biofilm formation and minimize sepsis development .

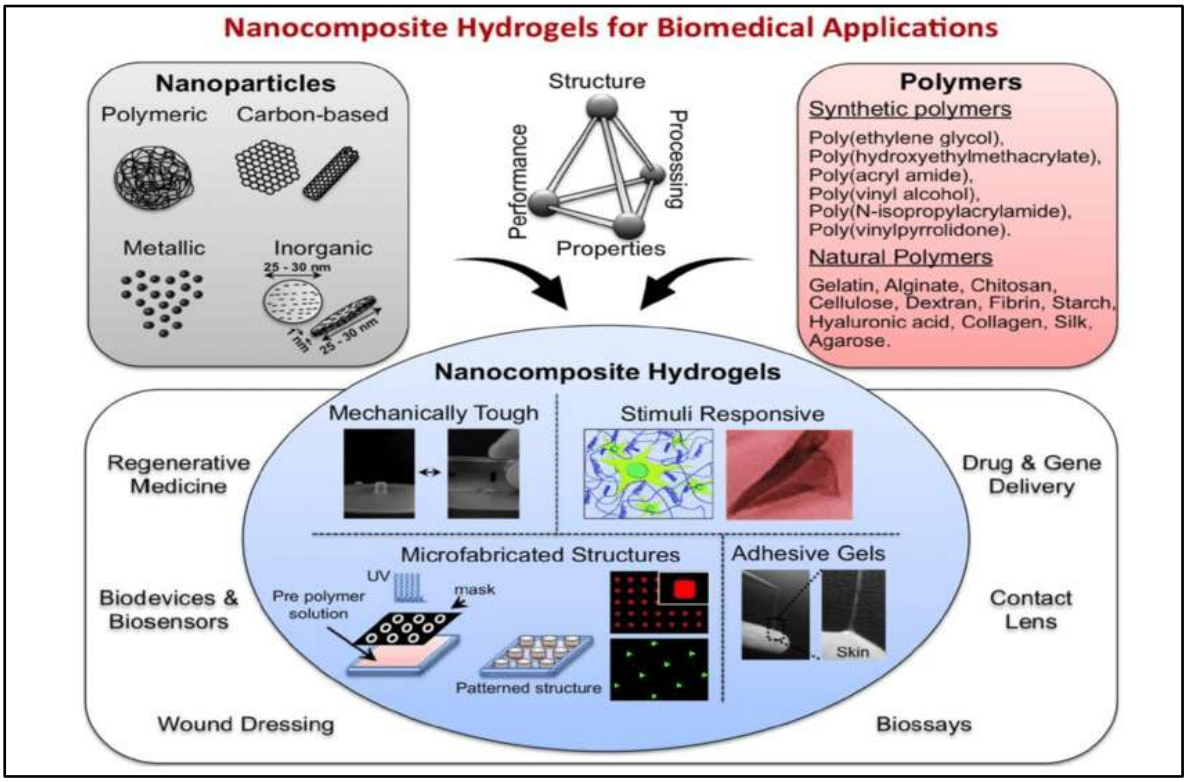

Fig. 2. Nanocpomposite Hydrogel

II. CONCLUSION

Scientific innovation in biomedicine occurs via collagen peptide-based nanocomposite hydrogels which support tissue construct development and pharmaceutical delivery systems and bioengineering medicine applications. The advanced materials serve as extracellular matrix mimics by supporting cell adhesion during their process of controlled cell growth and differentiation and mechanical functionality.Nanocomposite collagen hydrogels demonstrate great potential for personal medicine advances and improved therapeutic applications due to advancements in scientific challenges.

REFERENCES

[1]. Landis WJ. An overview of vertebrate mineralization with emphasis on collagen-mineral interaction. Gravit Space Biol Bull.1999;12(2):15–26.

[2]. Ottani V Raspanti M, Ruggeri A. Collagen structure and functional implications. Micron.2001;32(3):251–260.
[3]. Tzaphlidou M. The role of collagen in bone structure: An image processing approach. Micron.2005;36(7–8): 593–601.
[4]. Yamanlar S, Sant S, Boudou T, Picart C, Khademhosseini A. Surface functionalization of hyaluronic acid hydrogels by polyelectrolyte multilayer films. Biomaterials.2011;32(24):5590– 9.
[5]. Madihally SV, Matthew HWT. Porous chitosan scaffolds for tissue engineering. Biomaterials.1999; 20(12): 1133–1142.
[6]. Patel A, Xue Y, Hartley R, Sant V, Eles JR, Cui XTet al. Hierarchically aligned fibrous hydrogel films through microfluidic self-assembly of graphene and polysaccharides. Biotechnology and Bioengineering.2018; 115(10): 2654–2667.
[7]. Gelse K, Pöschl E, Aigner T. Collagens-structure, function, and biosynthesis. Adv Drug Deliv Rev. 2003;55(12):1531-1546.
[8]. Dong C, Lv Y. Application of collagen scaffold in tissue engineering: recent advances and new perspectives. Polymers (Basel). 2016;8(2):42.
[9]. de Miranda RB, Weimer P, Rossi RC. Effects of hydrolyzed collagen supplementation on skin aging: a systematic review and meta-analysis. Int J Dermatol. 2021;60(12):1449-1461.
[10]. Wang H, Tu Z, Wang Hui. Preparation of high content collagen peptides and study of their biological activities, Food Res Int. 2023;174:1
[11]. Parvizi M, Plantinga JA, Van Speuwel-Goossens CA, Van Dongen EM, Kluijtmans SG, Harmsen MC. Development of recombinant collagen-peptide-based vehicles for delivery of adipose-derived stromal cells. J Biomed Mater Res A. 2016;104(2):503-16.
[12]. Knapinska AM, Tokmina-Roszyk D, Amar S, Tokmina-Roszyk M, Mochalin VN, Gogotsi Yet al. Solid-phase synthesis, characterization, and cellular activities of collagen-model nanodiamond-peptide conjugates. Biopolymers. 2015;104(3):186-95.
[13]. Pastar I, Stojadinovic O, Golinko MS, et al. Epithelialization in wound healing: A comprehensive review. Adv Wound Care. 2014;3(7):445-464.
[14]. Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. Adv Wound Care.2015;1;4(9):560-582.
[15]. Waqar MA, Mubarak N, Khan AM, Shaheen F, Mustafa MA, Riaz T. Recent advances in polymers, preparation techniques, applications and future perspectives of hydrogels.Int J Polym Mater.2024;74(4):265-284.
[16]. Chu W, Nie M, Ke X, Luo J, Li J. Recent advances in injectable dual crosslinking hydrogels for biomedical applications.MacromolBiosci. 2021;21(7):
[17]. KasaiRD, Radhika D, Archana S, ShanavazH.A review on hydrogels classification and recent developments in biomedical applications. Int JPolym Mater. 2022;72(13):1-11.
[18]. Ho TC, Chang CC, Chan HP, Chung TW, Shu CW, Chuang KPet al. (2022). Hydrogels: properties and applications in biomedicine. Molecules 2022;27(9):2902.
[19]. Vasile C, Pamfil D, StoleruE, Baican M. New developments in medical applications of hybrid hydrogels containing natural polymers. Molecules.2020;25(7):1539.
[20]. Li J, Mooney DJ. Designing hydrogels for controlled drug delivery. Nat Rev Mater. 2016;1(12):16071.
[21]. Hoffman AS. Hydrogels for biomedical applications. Adv Drug Deliv Rev. 2012;64:18-23.
[22]. Peppas NA, Hilt JZ, Khademhosseini A, Langer R. Hydrogels in biology and medicine: From molecular principles to bionanotechnology. Adv Mater. 2006;18(11):1345-60.
[23]. Ligong Lu; Leung Chan; Bing Liu, et al.Functional hydrogels for hepatocellularcarcinoma: therapy, imaging, and in vitro model.Xuet al. Journal of Nanobiotechnology.2024;22:381.
[24]. Sonwane SM, Ingle R. Recent advances in hydrogel drug delivery systems: innovations and applications. Int J Drug Del Tech. 2024;14(4):945-947.
[25]. Liu B, Chen K. Advances in Hydrogel-Based Drug Delivery Systems. Gels. 2024; 10(4):262.

[26]. Fairbanks BD, Singh SP, Bowman CN, Anseth KS. Photodegradable, photoadaptable hydrogels via radical-mediated disulphide fragmentation reaction. Macromolecules. 2011;44(8):2444.
[27]. Xu J, Liu Y, Hsu S. Hydrogels based on schiff base linkages for biomedical applications. Molecules.2019;24(16):3005.
[28]. GoundenV, Singh M. Hydrogels and wound healing: current and future prospects. Gels. 2024;10(1):43.
[29]. Diniz FR, Maia RCAP, Rannier L, Andrade LN, Chaud MV, da Silva CF et al. Silver Nanoparticles-Composing Alginate/Gelatine Hydrogel Improves Wound Healing In Vivo Nanomaterials 2020, 10, 390
[30]. Zhang WL, Yang X, Yang K, FuYV, Xu T, Li S. A novel double-crosslinking-double-network design for injectable hydrogels with enhanced tissue adhesion and antibacterial capability for wound treatment. Adv Funct Mater. 2019;30(1).
[31]. WangL, Duan L, Liu G, Sun J, Shahbazi MA, Kundu SC et al. Bioinspired polyacrylic acid-based dressing: wet adhesive, self-healing, and multi-biofunctional coacervate hydrogel accelerates wound healing. Adv Sci.2023;10(16): https://doi.org/10.1002/advs.202207352
[32]. Nawaz A, Ullah S, Alnuwaiser MA, Rehman FU, Selim S, Al Jaouni SK et al. Formulation and evaluation of chitosan-gelatin thermosensitive hydrogels containing 5FU-alginate nanoparticles for skin delivery. Gels.2022;8(9):537.
[33]. Li Y, DongX, Yao L, Wang Y, Wang L, Jiang Z Qiu, D et al. Preparation and characterization of nanocomposite hydrogels based on self-assembling collagen and cellulose nanocrystals. Polymers. 2023;15: 1308.
[34]. Asadi N, Alizadeh E, Bakhshayesh ARD, Mostafavi E, Akbarzadeh A, Davaran S. Fabrication and in vitro evaluation of nanocomposite hydrogel scaffolds based on gelatin/PCL–PEG–PCL for cartilage tissue engineering. ACS Omega. 2019;4 (1): 449-457