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RESEARCH ARTICLE

Fibrin-Based Biomaterials for Wound Healing: Innovations in Hydrogels, Sealants, and Dressings

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Abstract: Fibrin, a natural biopolymer derived from fibrinogen during the coagulation cascade, plays a fundamental role in haemostasis and tissue regeneration. This review highlights the multifaceted applications of fibrin-based biomaterials—including hydrogels, sealants, and dressings—in supporting the wound healing process. Fibrin matrices facilitate key biological functions such as cell migration, angiogenesis, and extracellular matrix (ECM) formation, which are essential during the haemostasis, inflammatory, proliferative, and remodeling phases of wound repair. Innovations in fibrin composites and hydrogel formulations have expanded their potential for controlled drug delivery, enhanced bioactivity, and scaffold engineering. Moreover, the integration of fibrin with nanomaterials like silver nanoparticles and biopolymers such as collagen and alginate has demonstrated improved structural integrity and antimicrobial activity. Despite significant advancements, challenges such as limited mechanical strength, rapid degradation, and scalability issues persist. This review also identifies existing research gaps and proposes future directions involving composite systems, nanotechnology integration, and personalized wound care approaches to optimize fibrin-based therapies in clinical settings.

Keywords: Fibrin-based biomaterials; wound healing; fibrin hydrogels; drug delivery; nanotechnology; regenerative medicine.

INTRODUCTION

FIBRIN-BASED BIOMATERIALS

The human body's largest organ, the skin has surface area 1.5 – 2m^{2}and approximately 15% of an individual's weight. The skin plays multiple roles, including regulating body temperature, protecting against mechanical damage, ultraviolet radiation, harmful chemicals and pathogens, retaining salts and fluids, providing insulting and sensory receptors and synthesizing vitamin D. The skin is the most peripheral part of the immune system. The skin comprises three layers: the epidermis, dermis and hypodermis. The epidermis – the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale while the dermis which is a thicker inner layer of the skin which contains blood vessels, lymph vessels, hair follicles, sweat glands, collagen bundles, various cell types – fibroblast, and nerve endings. The dermis primarily provides structure and support to skin but also serves to bind water, assist om thermal regulation, which protect the organism from mechanical injury, and the repair the skin. The vascular network within the dermis provides for the skin nutrition while the nerve endings is mediate the sensation of pain, touch and the temperature[1]. Fibrin (F) a natural protein formed during the blood coagulation cascaded plays a vital role in initiating haemostasis and wound healing. It facilitates cellular attachments cell proliferation and extracellular matrix formation, making it highly suitable for regenerative medicine applications. Due to its biocompatible and biodegradable nature, fibrin has emerged as a promising biopolymer for accelerating tissue regeneration. Fibrin and fibrin gel have been employed to deliver antibiotics in a localized and gradual manner aiding in infection control and enhancing healing[17].

MECHANISM OF WOUND HEALING THROUGH FIBRIN

Wound healing as a part of a natural process. Wound healing is a complex and continuous process which involves the four phases i.e. the – Haemostasis, inflammation, proliferation, and remodeling**Figure 1**. At each stages process as accurately and regularly but if due to some interruption, abnormality and prolongation of any process it can lead to delayed the wound healing and chronic wounds which do not heal it normally.

After an injury the haemostasis phase, starts immediately which involves the platelet accumulation which triggers the coagulation cascade which helps to stop bleeding at the site of injury then the inflammatory phase which lasts for 1 – 3 days in which the immune system are activated in order which to prevent the wound infection and release of mast cells inflammatory mediators like 5 – hydroxy tryptamine (5- HT) and histamine in which the increase of the blood vessel permeability at the wound site and promote the migration of neutrophil, monocytes, and the chemokines to the site of injury which leads to an inflammatory response, among them the monocytes that go to the wound tissue undergoes the differentiation into the macrophages in the response to the specific local environment and the inflammatory mediators cells are

the essential for the removal of necrotic tissue and foreign bodies as well as the initiating and the controlling wound process healing.

During the proliferation phase 4 – 21 days of wound healing in this the tissue formation characterized by the reepithelialization, angiogenesis, fibroplasia and wound contraction and the M2 macrophages population takes on a corresponding phenotype in which it is marked by the released of various growth factors (GFs) which including platelet- derived growth factors (PDGFs), tumor growth factor β1 (TGF -β1), vascular endothelial growth factor α (VEGF-α), platelet factor 4 (PF4) etc, and these chemotactic factors stimulate fibroblasts, endothelial cells and keratinocytes in surrounding tissues to initiates migration and proliferation. These myofibroblasts brought to a wound site transform into the myofibroblasts. These fibroblasts are the key players in the wound healing process and the contributing to the creating scar tissue through the synthesis and the arrangement of the collagen and the ECM components in which the eventually creates a protective barrier between the wound and the surrounding environment and leading to the wound closure.

Finally, the remolding occurs over a period of several months and the during which the dermis responds to the injury with the production of collagen and matrix protein and then returns to its pre – injury phenotype and the deposits in the wound will leads to some tissue dysfunction, regardless of the affected organ [2,3]

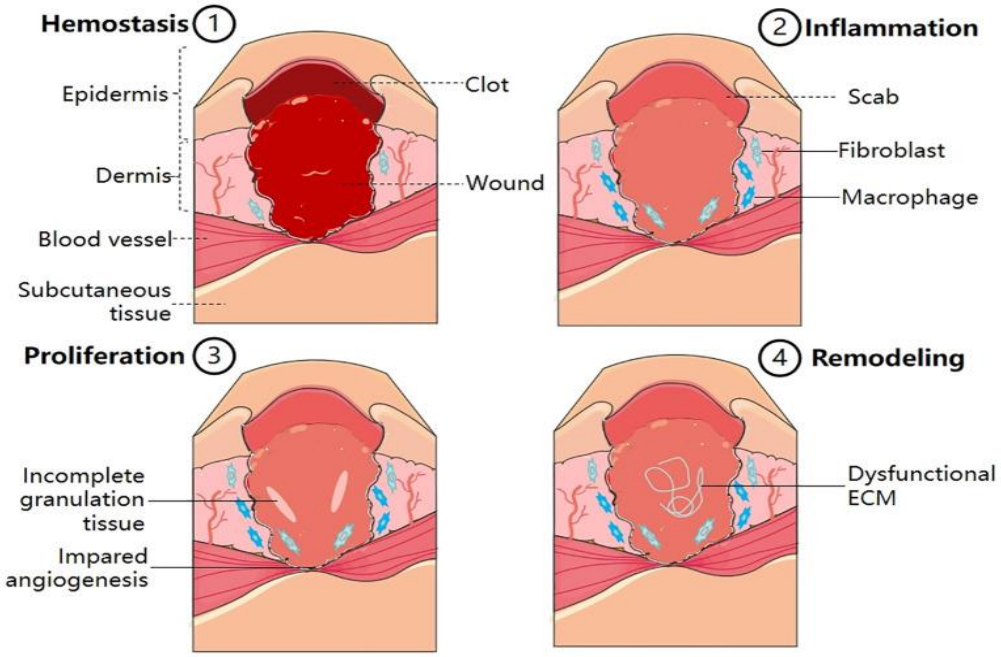

Figure :1 wound Healing process in 4 stages

HaemostasisPhase: Fibrin clot formation and platelet aggregation, Role of thrombin in fibrin polymerization. Inflammatory Phase: Fibrin as a scaffold for immune cell migration, Interaction of fibrin with macrophages and neutrophils. Proliferation Phase: Fibrin's role in fibroblast migration and angiogenesis, Release of growth factors (VEGF, PDGF, FGF) from the fibrin matrix. Remodeling (Maturation) Phase: Fibrin degradation by plasmin and tissue remodeling, Role in extracellular matrix (ECM) formation

COMPARISON WITH OTHER BIOMATERIALS IN WOUND HEALING

The serious complication can occur only when in the absence of adequate treatment or if the natural wound healing process becomes compromised. Normal wound healing follows pattern involving a series of complex steps that support the repair of damage tissues in anamount of time within the thirty days or less, depending on size and location. Fibrin matrix during wound healing provides attachment sites for cells, which in turn lay out a novel extracellular matrix, which is composed predominantly ofcollagen[4]. Biomaterials for wound healing is rich in biopolymers/ biomolecules, in which it can increases the rate of wound healing. Now these biomaterial plays numerous roles in regenerative medicine, tissue engineering, biosensors, bio templates, and many more are recent advances in biomaterials have provided opportunities for clinical uses[8].

FIBRIN HYDROGELS FOR WOUND HEALING

First hydrogels used in the biomedical context appeared in the 1970's when the need for a new material for cell cultivation was high. An ideal haemostatic adhesive should deliver fast gelation, strong adhesion, biocompatible, biodegradable, and stability. Fibrin glue which composed of fibrinogen and thrombin, swiftly forms fibrin network in which is crucial for

providing a physical barrier. However, the component of thrombin is related to thrombogenic risk and the storage instability and inherently weak adhesion of fibrin glue restricts its effectiveness for haemostatic application[5].Hydrogel gained significant attention in the field of wound dressing because due to its intrinsic hydrophilic 3D network. This network allows them to absorb wound exudates and create a moist environment that promotes wound healing. Hydrogel possess helpful characteristics which including the biocompatibility, biodegradability, non - toxicity, lack of allergenicity, ease of application and removal of high-water content which making them suitable as transdermal drug delivery carriers. The hydration effect by hydrogels on the skin which enhances the penetration of the therapeutics across the skin which clear the way for the transdermal delivery drugs. The drugs and therapeutic agents can be incorporated into the porous and the crosslinked the polymer network of hydrogels which allowing for the controlled release through modulation of the hydrogel's porosity, crosslinking degree and the swelling behaviour **Figure 2**. The external environment stimuli such as temperature and pH can trigger the drug release by modifying the chemical properties of the hydrogels[6].

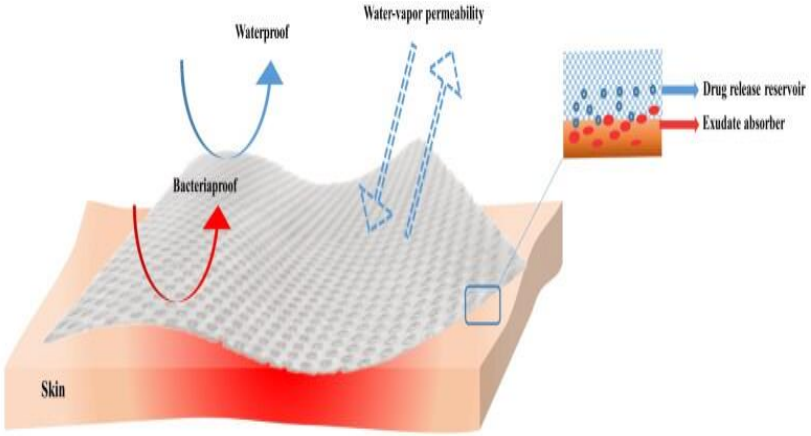

Figure 2 – Properties of hydrogel as a potential wound dressing for wound healing[6].

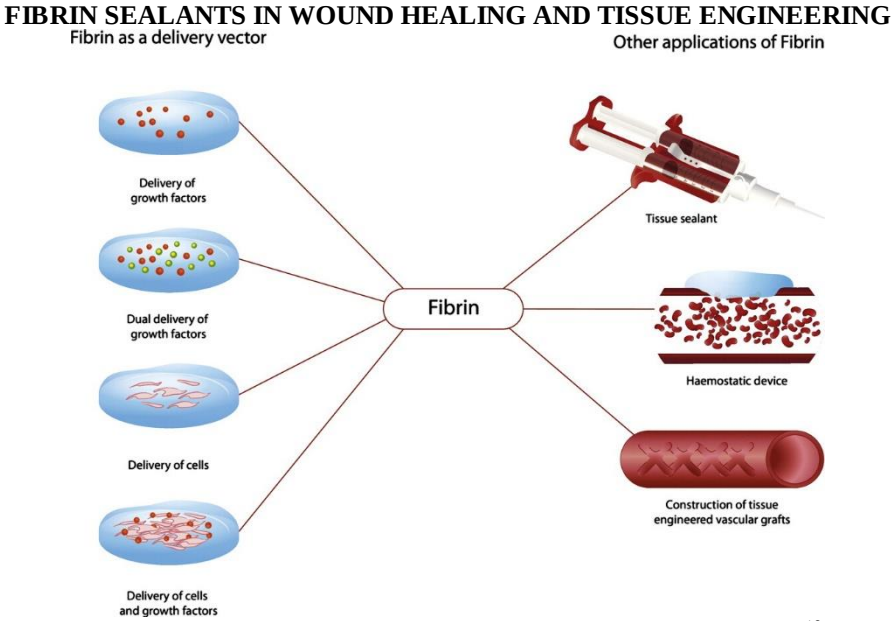

Figure 3: Fibrin Sealants in Wound Healing and Tissue Engineering[10]

Fibrin is formed in body from initiation of the clotting cascade and is produced commercially for use as a tissue sealant and haemostasis device during surgical procedures. By experimentally fibrin is being increasingly used as a vector to deliver growth factors cells, drugs and genes in tissue engineering applications of extra cellular matrix **Figure 3[9]**. Fibrin exceptional advantage over the other biomaterials which makes it ideal candidate for bone tissue engineering applications. Its nature is to nano - scaffold is following the tissue injury to initiate haemostasis and provide a temporary structure that can facilitates cellular activities and also deposition[10].

Fibrin sealants have been used successfully in the management of haemostasis and wound healing for following surgery and both as an adjunct and independently. Sealants possess extensive tissue adhesive strength and simultaneously reduce

haemorrhage and inflammatory responses. They are biocompatible and can be used for the slow delivery of drugs or growth factors to facilitate wound healing at the site of surgery. Since both the adhesive and the byproducts of its breakdown are biocompatible, fibrin sealants most closely resemble the ideal tissue adhesive. Fibrin sealants typically comprise two components – fibrinogen and thrombin – delivered through a dual – syringe system. When combined in the presence of calcium ions at the surgical site, rapid clot formation occurs within seconds with the clot naturally resorbing in 1- 2 weeks. Variations in fibrinogen and thrombin concentrations significantly influence the clot's (enhance shear/ tensile strength), while elevated thrombin accelerates clotting and enhances adhesion. The inclusion of factor XIII and adhesive glycoprotein further increases tensile strength and stability, providing tailored performance depending on clinical needs[11].

Fibrin – based biomaterials which include hydrogels, sealants, and dressings - which plays a foundational role in wound healing by forming a provisional matrix that supports haemostasis, cell migration, angiogenesis and controlled growth factor delivery. As natural hydrogels which derived from fibrinogen – thrombin systems, they enable tunable mechanical strength and degradation profiles depending on formulations e.g. fibrinogen, thrombin and factor XIII concentration. Innovation in fibrinogen hydrogel have focused on embedding therapeutic agents – including antibiotics, cells and cytokines – for sustained, localized delivery without provoking inflammatory response. Moreover, the development of fibrin composites e.g. nanofibers, nanoparticles, films which enhances scaffold stability, cell – binding affinity, and mechanical performance, essential for applications in dressings and regenerative matrices. These multifaceted designs illustrate how fibrin – based system are being optimized for advanced wound care applications, balancing biodegradability, bioactivity and clinically relevant material properties[12].

FIBRIN-BASED DRESSINGS AND SCAFFOLDS

Fibrinogen and fibrin play central, intertwined roles in wound healing by regulating coagulation, fibrinolysis, inflammation, cell -matrix interactions and even tumor – associated neoplasia. Distinct interactive sites on fibrin(ogen) – some concealed in fibrinogen and others revealed during polymerization – govern binding to thrombin, plasminogen/tPA, factor XIII, growth factors, platelets, leukocytes, fibroblasts, and endothelial cells. Fibrin polymerization initiates through thrombin – mediated cleavage of fibrinopeptides, followed by knob – hole assembly into protofibrils and lateral aggregation, factor XIIIa – mediated cross – linking further stabilizes a 3D fibrin network whose fibre thickness, branching, porosity, and permeability directly influence angiogenesis, cellular infiltration, and degradation kinetics. These structure – function relationships underpin the design of fibrin hydrogels, sealants and dressings that combine haemostatic scaffolding with tailored degradation and bioactive delivery properties. Fibrin polymerization encompasses a number of successive reactions, each affecting the ultimate structure and properties of the fibrin framework **figure 4**[13].

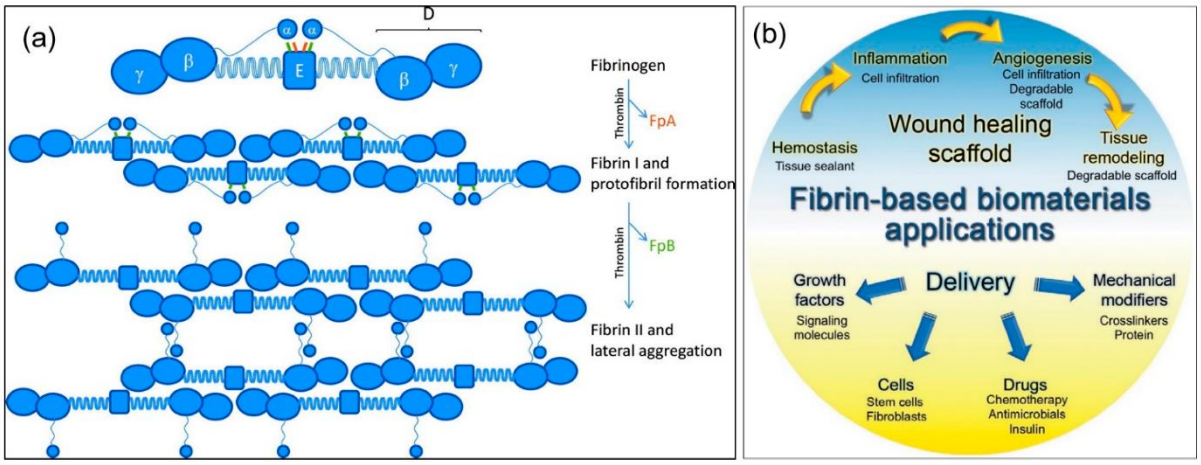

Figure 4: a) Fibrinogen to fibrin formation. B) Application of Fibrin based biomaterial[13]

Fibrin formed from fibrinogen by thrombin during the coagulation cascade, creates a mesh that traps platelets and immune cells, initiating clot formation and haemostasis. Platelet- derived growth factors subsequently recruit fibroblasts, promoting ECM synthesis- primarily collagen I and fibronectin – which facilitates tissues repair. Clinically, fibrin is applied as gels, glues or sealants often seeded with dermal fibroblasts to accelerate healing. Emerging research explores fibrin – based micro – and nanostructured scaffolds that better mimic native ECM. However, fibrin alone exhibits limited mechanical integrity and rapid degradation, which can be mitigated by blending it with synthetic or natural polymers to enhance scaffold stability and functionality[14].

FIBRIN WITH NANOTECHNOLOGY FOR WOUND HEALING

Nanomaterials possess unique characteristics due to the size and high surface area to volume ratio[15]. Silver has long been recognized for its potent broad – spectrum antimicrobial properties. Notably, silver – based dressings have demonstrated effectiveness without inducing bacterial resistance, making them a valuable asset in wound management. The literature identifies various chemical forms of silver – such as silver oxide, silver nitrate, silver sulphate, silver salt, silver zeolite, silver sulfadiazine (SSD) and silver nanoparticles (AgNPs) – each with unique applications in clinical practice.

Historically, silver nitrate was among the earliest forms utilized, particularly before the eighteenth century, where it was employed in treating leg ulcers, epilepsy, acne and venereal infections. Contemporary research underscores the widespread application of silver compounds in both acute and chronic wound care. Acute wound applications include burns (partial – and full – thickness), second – degree burns, freshly grafted burns and surgical or traumatic wounds such as colorectal surgical wounds, pilonidal sinus and donor sites. Chronic wounds which including pressure ulcers, diabetes foot ulcers, and leg ulcers have also shown significant healing improvements with silver – based treatments. These findings highlight silver's versatility and sustained efficacy across a broad spectrum of wounds types and reinforcing its value in modern therapeutic protocols[16]. Chitosan (CH) a natural biopolymer derived from chitin, has gamered considerable attention in biomedical applications due to its multifunctional properties. Studies have reported that chitosan exhibits excellent soft adhesiveness, biocompatibility, biodegradability and haemostatic activity, along with notable antibacterial effects. These characteristics make chitosan an ideal candidate for various wound healing and tissue engineering application[17]. Fibrin glue has several

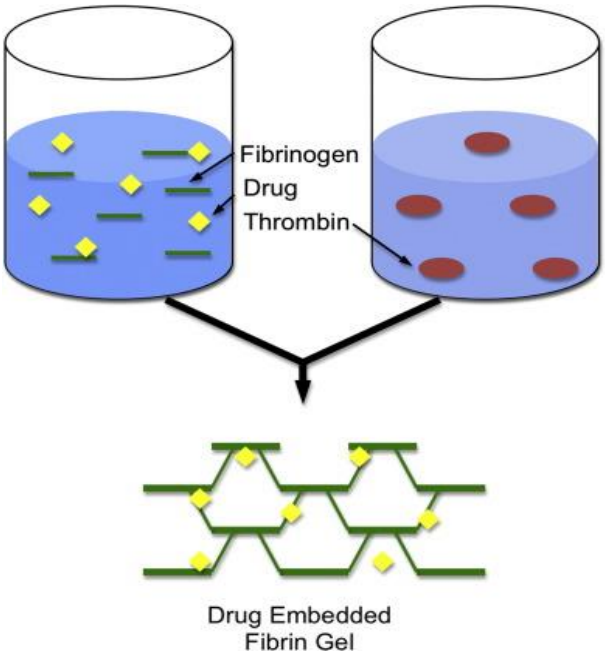

Figure 5: Fibrin with drug embedded attractive features which lend itself to the application of controlled release[18]**(Figure 5).**

FIBRIN IN COMBINATION WITH OTHER BIOMATERIALS

Fibrin and regeneration can promote the migration and ingrowth of cells. Fibrin and collagen are an ideal biomaterial for hydrogel scaffolds, because of their distinguished biocompatibility and cell adhesion capability[2]. Complex reaction occurs in a tissue like system could not properly investigated at the time. Material like collagen, alginate and carrageenan were used as an immobilization matrix for fibroblasts and microbial cells.Classical hydrogels with excellent biocompatibility and bioactivity are natural protein - based polymers like collagen, gelatine, silk fibrin and fibrin. Protein from extracellular matrix (ECM) like collagen or fibrin are promising candidates in the field of tissue implants due to their ability to mimic key biochemical factors vital for the tissue regeneration[7].Fibrin has gained significant attention in wound healing applications due to its natural abundance during the intrinsic wound repair process and its ability to modulate key reparative cellular functions. It possesses both vasculogenic and anti – inflammatory properties, making it a promising candidate for promoting tissue regeneration. Despite these advantage the fibrin's inherent mechanical compliance and fragility pose challenges in clinical handling and implantation. Moreover, the current clinical formulations often employ fibrin clotting components at supraphysiological concentration, leading to rapid gelation kinetics that may impose mechanical stress on encapsulated cells, potentially compromising cell viability and functionfigur(Figure,6)[19].

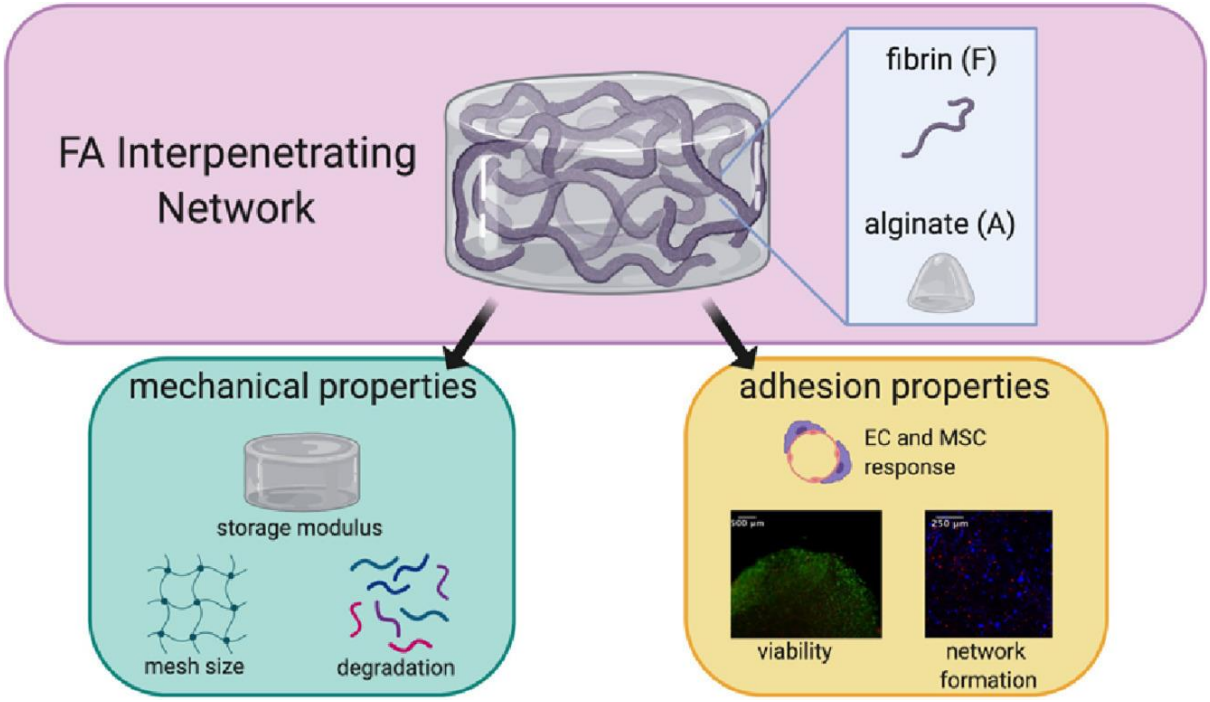

Figure 6: Fibrin-alginate hybrid biomaterials

Collagen and fibrin are two principal components of the extracellular matrix (ECM), contributing significantly to the structural integrity and mechanical strength of various tissues. Both biomolecules are co – localized within wound environments and play pivotal roles in the healing process. Due to their biocompatibility, biodegradability and clinical safety, collagen and fibrin have been widely utilized as individual biomaterials in diverse therapeutics contexts. Furthermore, their combination in the form of fibrin – collagen composites has demonstrated enhanced functional synergy, supporting a range of biomedical applications. These composites scaffolds have been particularly valuable in wound healing, regenerative medicine, and tissue engineering. Investigating the mechanical and structural characteristics of fibrin – collagen matrices is of considerable practical interest, as such composites have been shown to function effectively as haemostatic agents[20].Hydrogel have good biocompatibility, and it can prevent the loss of water and body fluid from wounds and owning to their biodegradability, secondary damage during the dressing can be avoided. Fibrin hydrogels are commonly synthesized through the combinations of fibrinogen and thrombin solutions at a 1:1 volume ratio, effectively mimicking the natural coagulation process in vivo. Upon mixing, thrombin enzymatically cleaves fibrinopeptide A from the N- terminal region of the α – chain and fibrinopeptide B from the β – chain within E domain of fibrinogen. This cleavage leads to the formation of the fibrin monomers, which spontaneously assemble via non – covalent interactions into soluble fibrin polymers. In the presence of calcium ions, these polymers rapidly undergo covalent crosslinking between adjacent fibrin molecules, resulting in the formation of an insoluble, stable fibrin hydrogel. Notable, this gelation process is rapid typically completing within seconds and closely resembles physiological haemostasis (Figure 1A). The microstructural analysis of the resultant fibrin hydrogel scaffold, as observed by field – emission scanning electron microscopy (FESEM), revealed a porous, three – dimensional mesh network (Fig 1B), characteristic of extracellular matrix – like architecture. This structural property is critical for supporting cellular infiltration nutrient diffusion and tissue integration. Biocompatibility was assessed using the CCK – 8 assays, which demonstrated that human umbilical cord – derived mesenchymal stem cells (hUC – MSCs) seeded within the fibrin hydrogel extract exhibited no apparent cytotoxicity indicating its biological safety. Degradation studies further highlighted the hydrogel's suitability for tissue engineering applications. The crosslinked fibrin scaffold underwent gradual degradation into fibrin degradation products (FDPs) (Fig. 1D). Structural integrity was maintained for approximately one week, with significant degradation occurring over the following week (Fig. 1E, F), demonstrating a favourable biodegradation profile.

Collectively, these findings underscore the potential of fibrin hydrogels as biocompatible, biodegradable scaffolds with a porous 3D microstructure conducive to cell adhesion and proliferation. Such properties make fibrin hydrogels promising candidates for applications in regenerative medicine and tissue engineering **figure 7**[21].

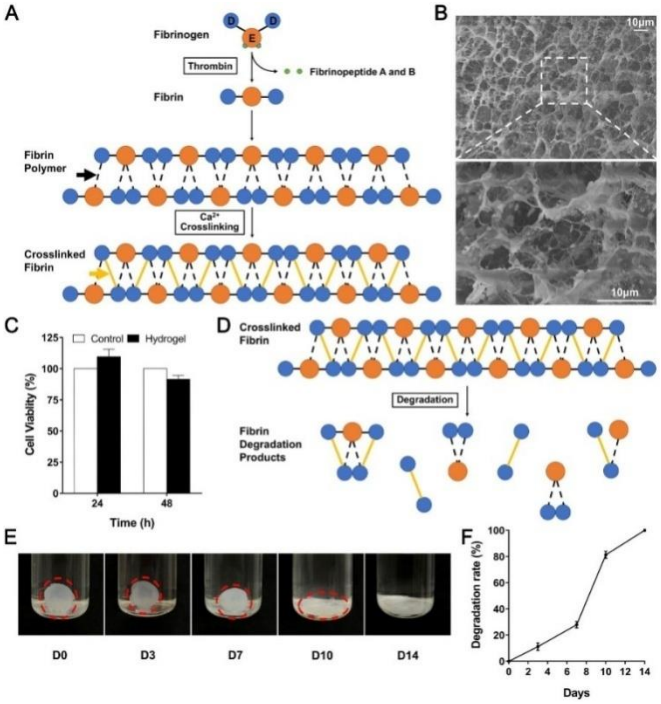

Figure 7: Synthesis and characterization of fibrin hydrogel scaffold

CONCLUSION

Fibrin – based biomaterial – including hydrogels, sealants and dressings which plays a crucial role in all four phases of wound healing: haemostasis, inflammation, proliferation and remolding. Their natural biocompatibility, biodegradability and ability to support cellular migration, angiogenesis and extracellular matrix (ECM) formation make them highly suitable for regenerative medicine. Fibrin hydrogels offer tunable mechanical and degradation properties enabling controlled drug deliver and enhanced healing environments. Sealants provide effective haemostatic and adhesive capabilities in surgical settings, while fibrin – based dressings and scaffolds especially when combined with materials like collagen, alginates and chitosan, enhance structural integrity and bioactivity. Integration with nanotechnology, such as silver nanoparticles has further expanded the antimicrobial potential of fibrin – based wound care strategies.

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