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Skin Patch for Rehabilitation of Diabetic Foot Ulcers

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ABSTRACT

Background of the study: Skin injuries are just one of the many existing challenges in the healthcare domain. Such a diverse range, from burns to chronic wounds, is diverting attention towards biomaterial-based approaches for wound healing, including hydrogels as a possible alternative to traditional methods using tissue-engineered skin grafts. However, serious skin injury rehabilitation, like diabetic foot ulcers, requires further research and compelling advanced solutions that underline the importance of wound healing and recovery.

Methodology: Hydrogel blends were prepared using Polyvinyl Alcohol (PVA) and Polyethylene Glycol (PEG) solutions, and combining them in a specific 75:25 ratio. Glutaraldehyde (GA) was added in varying amounts of 3%, 5%, and 8% to promote chemical cross-linking of the two polymers to achieve enhanced mechanical stability of the hydrogel films. Preliminary characterization tests were then conducted on all the samples to assess the physical properties of the synthesized hydrogel films.

Results: The PVA-PEG hydrogel films showed favorable results, with controlled degradation characteristics throughout the experimental period. The prolonged swelling and degradation properties of PVA-PEG hydrogel films may suggest suitable applications in wound healing scenarios. Therefore, this reflects the versatility of PVA-PEG hydrogels in dealing with innumerable skin injuries and their potential application for rehabilitation studies.

Conclusion: PVA-PEG hydrogel synthesis with the integration of GA provides an interesting approach being developed for skin rehabilitation, as it provides mechanical stabilization and controlled degradation. These hydrogels show great promise for innovative approaches towards wound healing, particularly in treating conditions such as diabetic foot ulcers. Future studies need to perform cytocompatibility and various biological tests to facilitate easy clinical translation and elucidate the potential of biomaterial-based methods in improving patient outcomes in wound care and rehabilitation.

Keywords: *Polyvinyl Alcohol, Polyethylene Glycol, Glutaraldehyde, Synthetic Skin, Hydrogel, Diabetic Foot Ulcer, Skin Rehabilitation, Tissue Regeneration.*

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INTRODUCTION

Skin is the largest organ of the human body that functions as a sensory detector, regulates body temperature, maintains fluid balance, senses pressure and pain, and the very consistency of skin is important for maintaining physiological equilibrium[1]. The skin consists of three main layers: Epidermis (outer layer), Dermis (inner layer), and Subcutaneous Tissue, as shown in Figure 1.

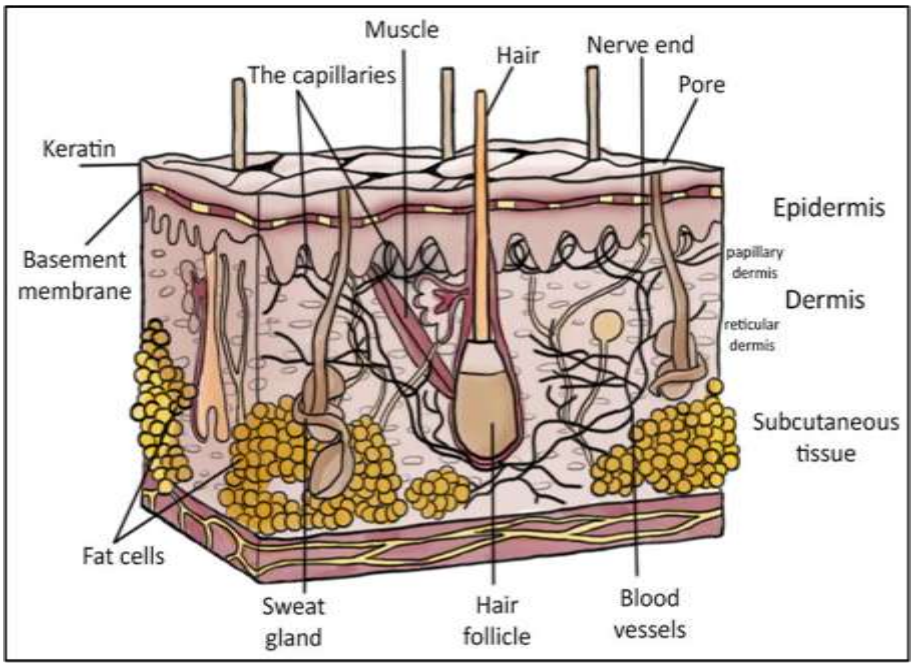

Figure-1 Illustration of the structural composition of the skin

The skin's outer layer, the stratum corneum, is mostly made of keratinocytes producing keratin, while the dermis is rich in proteoglycans, fibronectin, elastin, and collagen[2]. Skin is the body's first line of defense against environmental threats, e.g., UV radiation, chemicals, physical stresses, and diseases. Its protective role exposes it to various traumas from the external environment, causing wounds. Skin wounds can be as minor as a break in the epithelium or as severe as a wound that extends into the subcutaneous tissue and damages surrounding structures[3]. Furthermore, according to WHO data, around 11 million burn-related skin injuries occur each year, translating into approximately 180,000 deaths[4]. Recent interest in tissue-engineered skin grafts as substitutes for traditional treatments stems from their ability to mimic the skin's structure, crucial for effective healing[5].Skin grafting encompasses two main types: split-thickness (STSG) and full-thickness (FTSG). STSG involves the epidermis and part of the dermis, while FTSG includes the entire skin thickness. Grafts are classified by donor site as autograft, homograft, isograft, allograft, or heterograft/xenograft[6]. Autologous skin grafting, harvested from one's body, is common. Full-thickness grafts offer better cosmetic results but need a well-vascularized bed. Donor sites include post-auricular, pre-auricular, supra-clavicular, antecubital fossa, inguinal crease, and volar wrist crease skin[7].Autologous skin grafts, regardless of type, necessitate a vascularized wound bed and pose limitations in size due to the need for primary closure at the donor site. In acute wound treatment, expansion time may be prolonged, necessitating closure with a split-thickness graft from a third site. Limited donor availability further complicates this issue[7]. Hematoma and infection are common complications, with hematoma hindering graft bed contact and infection significantly reducing graft take rates, particularly with bacteria like S. aureus and Pseudomonas[8]. Skin grafts often yield suboptimal aesthetic results, with color, texture, and contour mismatches leading to a patch-like appearance, especially in small grafts adjacent to native facial skin. Split-thickness

grafts tend to contract over time, potentially affecting nearby anatomical structures[9]. Biomaterials interact with biological systems. Skin biomaterials are designed for wound repair, excel in biocompatibility, and regeneration[10]. Hydrogels are a kind of hydrophilic polymer with a cross-linked structure, efficiently absorbs water. Hydrogel dressings serve dual purposes: aiding wound closure and promoting tissue integration through regeneration[11]. This research explores using synthetic polymer hydrogels emulating human skin as an alternative treatment for severe skin injuries. Cross-linking the hydrogel with 25% aqueous Glutaraldehyde (GA) utilizing Polyvinyl Alcohol (PVA) and Polyethylene Glycol (PEG) results in a 75:25 PVA-PEG ratio blend. The FDA recognizes PVA and aliphatic polyesters, including PEG, as significant synthetic biodegradable polymers for human medical applications[12]. PVA hydrogels are popular in wearable technology and biological materials due to their excellent processability and biocompatibility in real-world use[13]. PEG is a biocompatible polymer with numerous applications in biotechnology and medicine, including tissue engineering[14]. Highly hydrophilic, PVA exhibits excellent solubility in water and organic solvents. Additionally, the addition of PEG enhances polyester chain mobility and acts as a plasticizer[15]. To facilitate cross-linking and encourage fixing, glutaraldehyde (OHC-(CH2)3-COH) is employed[16]. This research systematically investigates PVA-PEG hydrogels, analyzing their mechanical properties, morphological structures, and the impact of glutaraldehyde cross-linking. In addition to addressing general challenges in wound healing, this research investigates the potential of biomimetic polymeric films as an alternative approach for the rehabilitation of severe skin injuries such as foot ulcers due to diabetes[17]. Foot ulcers are a common and serious complication of diabetes, often leading to prolonged healing times, infections, and in severe cases, amputations. By focusing on innovative wound healing strategies, we aim to contribute to the development of effective treatments for diabetes-related skin injuries, ultimately improving outcomes and quality of life for affected individuals[18].

METHODOLOGY

Materials

Polyvinyl alcohol (PVA) (USP Reference Standard) from Sigma Aldrich. Polyethylene glycol (PEG) (Mw 8000) from Sigma Aldrich. 25% aqueous solution of Glutaraldehyde (GA) from Sigma Aldrich. Distilled water is used to dissolve the polymers.

Preparation of Phosphate Buffer Saline (PBS) Solution

To conduct the degradation test, the PBS solution was prepared by dissolving 1 PBS tablet in 800 ml of distilled water and then placing the solution in an autoclave at 121℃ for 15 minutes. The solution was then taken out and cooled down, and the pH of the solution was adjusted to 7.4 (the pH of blood) using dilute HCl acid. Following this, the volume of the PBS solution was adjusted to 1000 ml (1 liter) by adding distilled water.

Preparation of PVA-PEG and their hydrogel blends

In this research, polymer films were synthesized utilizing a meticulous methodology to ensure precision and reproducibility, as shown in Figure 2.

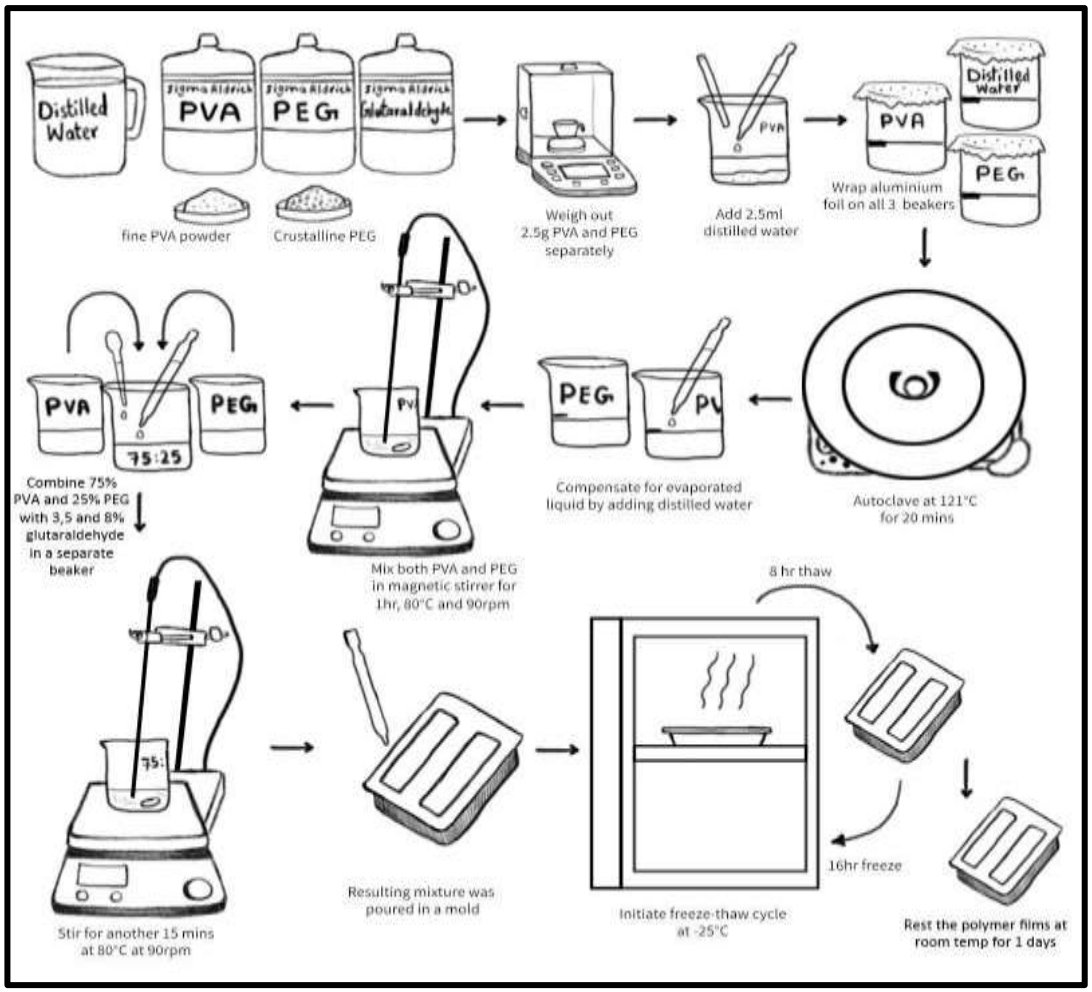

Figure 2: Methodology of creating a (75% PVA 25% PEG) polymer-based hydrogel blend

To create the PVA hydrogel, a PVA solution (10% w/v) was prepared by dissolving 2.5 gm of PVA powder in 22.5 ml of distilled water. To create the PEG hydrogel, a PEG solution (10% w/v) was prepared by dissolving 2.5 gm of PEG crystals in 22.5 ml of distilled water. Levels of both liquids were marked on the beaker using a permanent marker. The beakers were covered with perforated aluminum foil and were separately autoclaved at 121℃ for 20 minutes to ensure sterility. After being autoclaved, the levels of evaporated liquid were compensated by adding distilled water up to the previously marked levels, and subsequent stirring on a hot-plate magnetic stirrer for 1 hour at 80°C and 90rpm enhanced homogeneity. Three new beakers were utilized to combine 75% PVA solution (16.875 ml) with 25% PEG solution (5.625 ml), to which 0.673ml (3%), 1.125ml (5%), and 1.8ml (8%) of GA were each added, and stirred on a hot plate magnetic stirrer for an additional 15 minutes at 80°C and 90 rpm induced cross-linking. The mixtures were pipetted into silicon molds. The polymerization was initiated through six freeze-thaw cycles, each consisting of a 16-hour freeze at -25°C followed by an 8-hour defrost at room temperature. After six cycles, the polymer films were allowed to air dry at room temperature for 1 day. This comprehensive methodology ensures the controlled synthesis of polymer films, paving the way for subsequent analysis and application in this research[19].

Swelling and Degradation Tests:

A biodegradability test was performed on the samples to assess their level of swelling and degradation. PBS was used as it mimics the body fluids due to its similar osmolarity and ionic

concentration. The percentage weight change graph was developed using the data measured at varying time intervals until complete degradation occurs.

Contact Angle Test:
A contact angle test was performed to evaluate the measurements between a liquid droplet and the surface of the samples to determine if the samples were hydrophobic or hydrophilic.

Tensile Test:
The tensile test was performed on all three samples using a Universal Testing Machine (UTM) (JINAN XLC TESTING MACHINE CO., LTD) equipped with 2kN load grips. The samples were cut into rectangular shapes (0.5 inch-width/ 2 inch-length) and underwent stretching at the rate of 5mm/min till the point of breakage.

Statistical Analysis:
Swelling, degradation, and contact angle tests were performed in triplicate (n=3) and their data presented as mean ± standard deviation. Statistical analyses were performed using Excel's Analysis ToolPak (Microsoft 365) with the level of significance set to $\alpha=0.05$. Swelling kinetics were performed by Two-way ANOVA considering 3 factors: Time (10 mins to 3 weeks), GA concentration (3%, 5%, 8%), and their interaction. A Single-Factor ANOVA test was performed to analyze the degradation at fixed time intervals (10 mins, 24 hours, 1 week, 3 weeks), taking GA concentration as the independent variable. A Single-Factor ANOVA test was also employed to analyze the contact angle measurements. No post-hoc tests were done, being outside the scope of this initial characterization study.

RESULTS

Our pre-weighed sample was submerged in 7ml of PBS solution, as shown in ***Figure 3 (A, B, C)***.

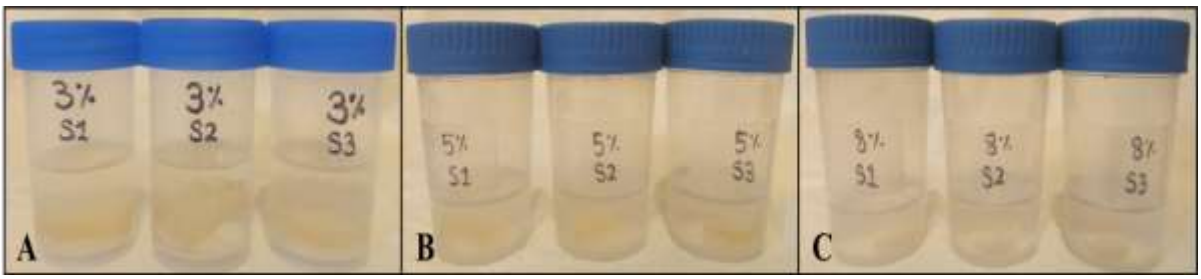

Figure-3 (A, B, C): Swelling and Degradation of PVA-PEG (75:25) hydrogel samples crosslinked with 3%, 5% and 8% GA, respectively

The percentage weight change graphs for the samples fabricated for PVA-PEG blends are shown in Figure 4 (A, B, C). As observed, the blend with 3% glutaraldehyde swelled for 2 days and started to degrade slowly; whereas, the blend with 5% and 8% glutaraldehyde swelled for 1 day, where 8% is degrading faster in comparison. The error bars were formed using the standard deviation, which shows how much the observed values deviate from the mean. Two-Factor ANOVA for swelling kinetics results indicate the presence of three statistically significant factors: time ($F=17.27$, $p<0.0001$), GA concentration ($F=276.93$, $p<0.0001$), and their interaction ($F=7.05$, $p<0.0001$). This interaction effect displays that the concentration-dependent swelling patterns diverged with time: 3% GA hydrogels showed peak swelling at 24 hours (1067.45 ± 283.39), whereas the 8% GA formulations maintained minimal swelling (<100% at all time points). Single-Factor ANOVA for degradation at different time intervals substantiated that this was a concentration-dependent effect for all time points at 10 mins ($F=6.66$, $p=0.030$), 24h

(F=27.09, p=0.00099), 1 week (F=51.46, p=0.00017), and 3 weeks (F=52.88, p=0.00015).

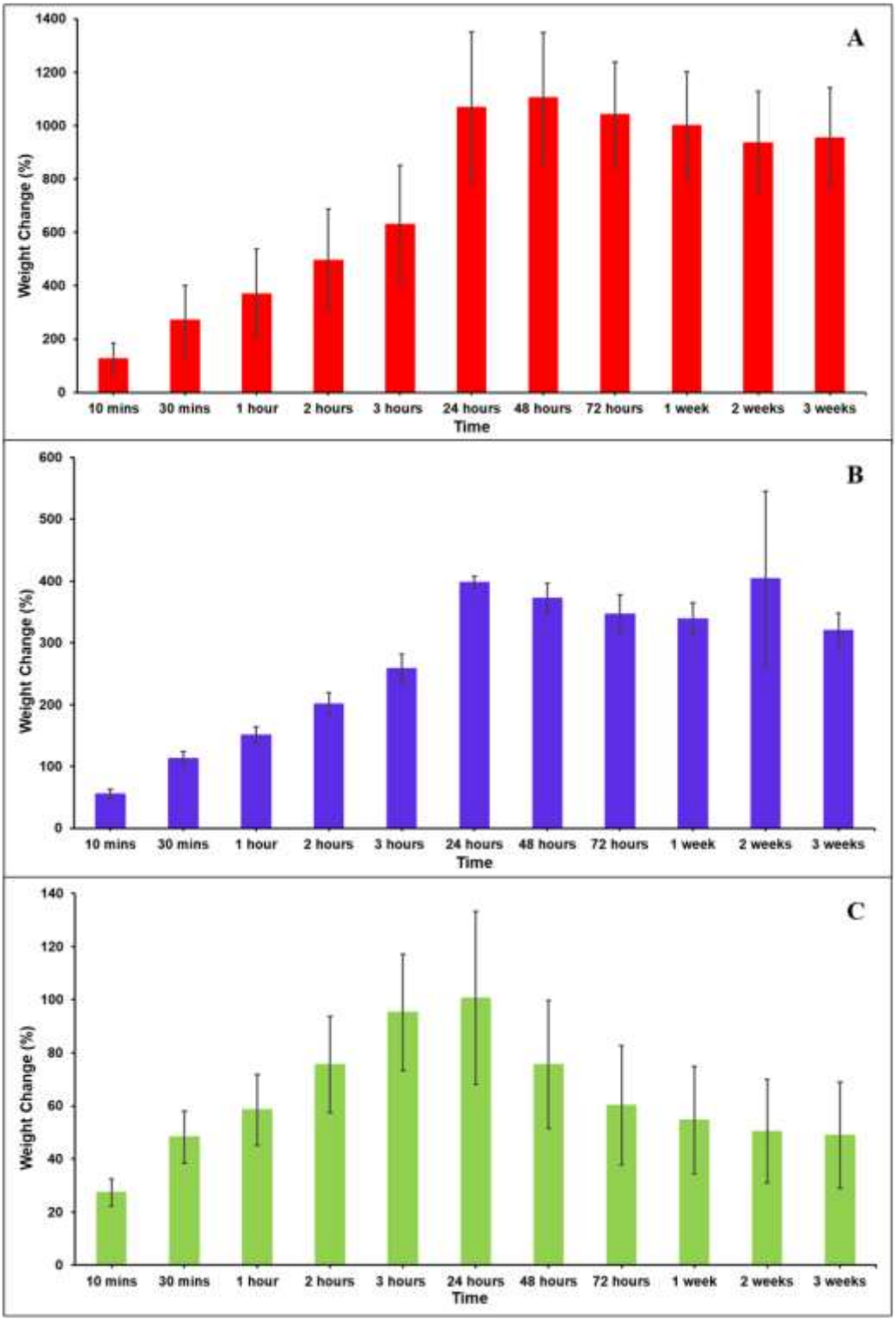

Figure 4 (A, B, C): Swelling and Degradation results of PVA-PEG (75:25) hydrogel samples crosslinked with 3%, 5%, and 8% GA under PBS solution over 3 weeks, respectively

Images were taken for different percentages of Glutaraldehyde (3%, 5%, 8%) as shown in Figure 5 (A, B, C). A 90° contact angle is frequently regarded as a threshold; a contact angle less than 90° indicates hydrophilicity, and more than 90° indicates hydrophobicity. To sum up, the averages of the results indicate that they are hydrophilic, as shown in Figure 6. Single-Factor ANOVA for contact angles indicated that no significant difference existed between concentrations (F=0.75, p=0.512). All formulations displayed hydrophilicity with respective mean contact angles below 90°: 3% GA (63.2±14.0°), 5% GA (69.0±5.1°), and 8% GA (75.7±15.8°). The similar hydrophilicity displayed by the concentrations indicates that GA crosslinking most likely affects the swelling/degradation characteristics in bulk and does not influence surface wettability.

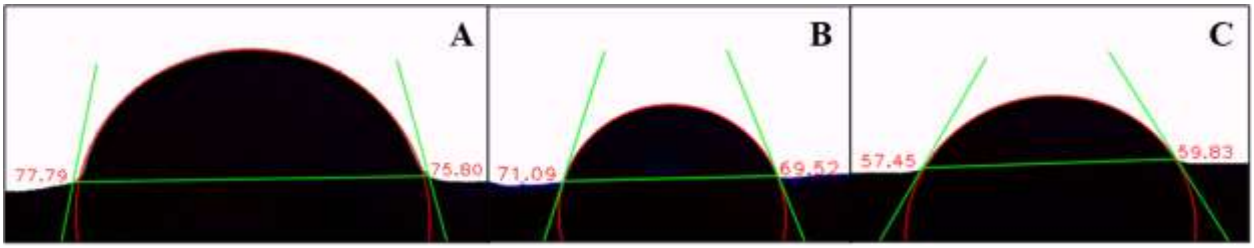

Figure 5: (A, B, C): Best computerized image of water droplet on PVA-PEG 3%, 5% and 8% GA Polymeric Film, respectively.

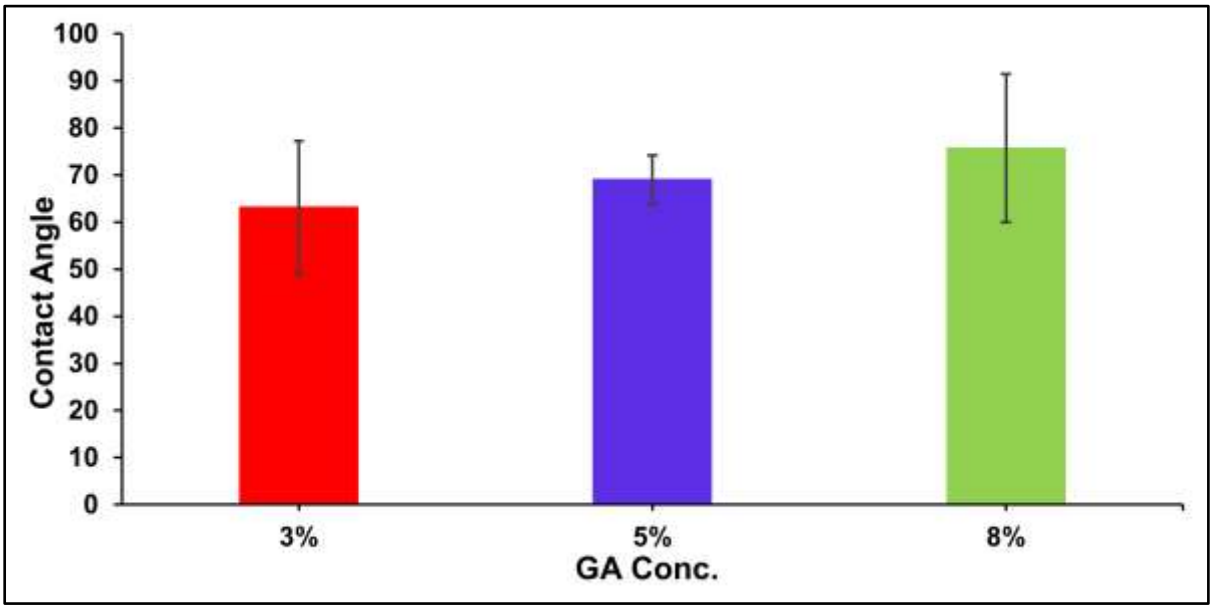

Figure 6: Averages of contact angle for each sample.

The tensile test was used to evaluate the mechanical properties of PVA-PEG 75:25 hydrogels crosslinked with varying GA concentrations (3%, 5%, and 8%). As shown in ***Table 1***, Sample B (5% GA) hydrogel exhibited the highest Young's modulus (8 MPa), indicating greater stiffness than the 3% and 8% formulations. While Samples A (3% GA) and B (5% GA) demonstrated similar tensile strength values (0.70 MPa and 0.639 MPa, respectively), Sample C (8% GA) exhibited a significantly lower value (0.30 MPa). Sample B also demonstrated the highest elongation at break (35.0%), suggesting better elasticity than the other formulations.

Table 1: Mechanical Properties of PVA-PEG (75:25) Hydrogels with varying GA concentrations.

Specimen	Young's Modulus (MPa)	Tensile Strength (MPa)	Elongation at Break (%)
A (3% GA)	4.0	0.70	27.5
B (5% GA)	8.0	0.639	35.0
C (8% GA)	2.8	0.30	16.5

DISCUSSION

In this research on PVA-PEG hydrogels, several aspects contribute to the uniqueness and potential superiority of this research work compared to existing studies. Notably, the focus on incorporating different percentages of GA as a crosslinker in the hydrogel synthesis process sets this work apart, which will further help us to determine, after further testing, which percentage of GA helps mimic the human skin best. The inclusion of GA enhances the cross-linking efficiency, leading to a more robust and stable 3D network. This approach aligns with recent advancements in hydrogel technology, emphasizing the importance of optimizing cross-linking methods for superior mechanical properties and increased resistance to degradation[20]. Additionally, the use of GA as a crosslinker has been proven effective in other studies involving hydrogel fabrication, supporting the decision to implement this method[21]. While GA crosslinking improves mechanical stability, its proven potential to make the material cytotoxic may deter its clinical translation[22]. In the case of DFU, dermal exposure to a cytotoxic dressing may cause skin irritation, discoloration, or even dermatitis, which was proven by exposure to 2.5% GA[23]. GA crosslinking can be optimized while minimizing its cytotoxic effects by either combining GA with other crosslinkers to reduce its concentration while obtaining the benefits of each crosslinker, or using post-crosslinking chemical treatments (e.g., glycine), which help mask the aldehyde groups introduced into the material through GA[24]. Moreover, this research investigates the degradation behavior of the PVA-PEG hydrogel through testing in PBS solution, its hydrophilic nature, and its mechanical strength. Understanding the degradation kinetics is paramount for tailoring hydrogels to specific applications. Statistical findings in this research suggest that GA concentration is an essential factor in modulating hydrogel swelling behavior. A highly significant interaction effect ($p<0.0001$, $F=7.05$) indicates that 3% GA formulations are time-dependent, where they swell up to about 24 hours of maximum absorption and then start gradually declining, while the 8% GA hydrogels had limited swelling due to high-density crosslinking. The extreme variation in swelling (up to 147142.14) for 3% GA indicates high chances of batch-to-batch inconsistency in crosslinking density, whereas 8% GA's low variance (718.66) would mean easy reproducibility. The trends supported statistically guided material choice for absorption: 3% GA is suited for high-fluid absorption, and 8% GA for low-swelling systems requiring structural stability. Additionally, the consistent hydrophilicity across GA concentrations ($p=0.512$) ensures sufficient fluid absorption regardless of the varying crosslinking density, which is an essential aspect of controlling exudate in diabetic foot ulcers. Thus, these statistically validated trends allow for a rational pathway by which to select hydrogels according to clinical requirements and highlight the importance of post-hoc comparisons and in vivo validation in future studies. The mechanical strength of the hydrogels helps determine which formulation will be best suited for specific applications, such as DFU treatment. In mechanical testing, Sample B (5% GA) showed the best result; however, Sample A (3% GA) also showed favorable results. Overall, choosing the most suitable formulation requires further testing, with additional results being considered during the final selection. By

systematically assessing swelling, degradation, hydrophilicity, and mechanical properties in a controlled environment, valuable insights are contributed to the stability and potential longevity of the hydrogel. This basic knowledge is meant to enable applications of sustained drug delivery or tissue engineering[25]. On a greater note, findings must be contextualized within the broad scope of wound healing and skin rehabilitation, as skin rehabilitation for severe injuries such as diabetic foot ulcers constitutes a great clinical problem. Diabetic foot ulcers are widely known for susceptibility to infection and delayed recovery, which often causes complications and prolonged recovery periods. Hydrogel-based fabrication, such as PVA-PEG blends, should offer forward-thinking solutions to accelerate wound healing and patients' recovery from diabetic foot ulcers[18]. The PVA-PEG-GA hydrogel, when compared with existing DFU therapies, has unique advantages and limitations in regards to three categories concerning wound dressings:

1. **Natural Polymer Dressings:** Collagen hydrogels promote angiogenesis, and chitosan shows intrinsic antimicrobial properties. However, these materials are also characterized by batch-to-batch variability and poor mechanical strength[26]. Our synthetic PVA-PEG system does not need donor dependence by way of reproducible chemical synthesis with GA cross-linking, yielding tunable degradation rates unmatched by natural polymers.
2. **Synthetic/Semi-Synthetic Dressings:** Our hydrogel benefited from the controlled polymer architecture, just like PEGDA-based systems, but unlike PEG networks, where pure PEG networks have mechanical stability, our hydrogel has been reinforced with PVA incorporation via freeze-thaw cycling[26]. However, high-end clinical alternatives such as PRP-loaded silk fibroin have exhibited bioactivity, a gap that our material must fill through future functionalization[27].
3. **Bioactive Dressings:** The modularity of our material provides a basis for further incorporation of bioactive agents, a strategic benefit for translational advancement, similar to advanced options such as GelMA-DFO systems that actively stimulate healing via growth factor delivery[27].

In addition, this research presents novel materials and processes for wound management, contributing to the field of rehabilitation sciences. This field adopts a multidisciplinary approach to enhance the function and quality of life for individuals living with disability or injuries. Within that framework, this research is continuing to prioritize improvement in wound healing outcomes through novel biomaterials and crosslinking approaches[17]. The increasing prevalence of diabetic foot ulcers across South Asia (5.5% regional average, ranging 3.1-11.6% in Pakistan) occurs against a backdrop of strained healthcare systems, with Pakistan ranking 154th in healthcare performance and facing significant resource limitations in DFU management[28,29]. The PVA-PEG-GA hydrogel's design directly responds to these challenges through three key features: (1) the freeze-thaw synthesis method, shown in *Figure 2*, enables production without specialized equipment, critical for regions with limited ulcer management centers; (2) the material's consistent quality addresses variability in care standards across facilities reporting DFU prevalence from 2.1-50.9%; and (3) the adjustable crosslinking density (3-8% GA concentrations) allows customization for different socioeconomic contexts, from urban clinics to rural primary care settings. With 33 million diabetics in Pakistan facing disproportionate complication risks due to healthcare access limitations, this synthetic approach offers a scalable solution that bypasses the cold chain requirements and supply chain instability that hinder biological dressing adoption in developing countries[28]. Current IWGDF guidelines emphasize three key principles for diabetic foot ulcer dressings: (1) selection based primarily on exudate control, comfort, and cost (strong recommendation), (2) avoidance of antimicrobial dressings used solely to accelerate healing (strong recommendation), and (3) consideration of sucrose-octasulfate dressings for difficult-to-heal neuro-ischemic ulcers (weak recommendation)[30]. Our PVA-PEG-GA hydrogel directly addresses these recommendations through its demonstrated swelling properties that may allow

controlled exudate management, synthetic composition that ensures cost-effective production, and avoidance of unnecessary antimicrobial additives. The guidelines also note that evidence supporting any specific dressing type remains limited due to small study sizes and methodological limitations[30]. This highlights the importance of our hydrogel's reproducible fabrication method, which overcomes the batch variability issues common in natural polymer dressings. Clinical practice recommendations further suggest selecting dressings that "minimize shear and friction" while considering patient preference and cost, criteria that the PVA-PEG hydrogel is designed to meet through its adjustable mechanical properties[31]. While advanced options like sucrose-octasulfate dressings show promise in clinical trials, our PVA-PEG-GA platform offers comparable potential for customized wound management without the high costs associated with many specialized dressings[30]. The hydrogel's synthetic nature and controllable degradation profile provide distinct advantages over natural polymer systems like collagen or chitosan, particularly in resource-limited settings where consistent quality and affordability are paramount[31]. The research into PVA-PEG hydrogels furthers the understanding of hydrogel properties and degradation kinetics while offering some promise for skin rehabilitation, wound healing, and recovery from diseases like diabetic foot ulcers. It resolves major wound management issues and, with the use of novel materials, seeks to impact rehabilitation sciences positively, thereby improving patient outcomes[17]. However, there are a few key limitations in this study: (1) No cytocompatibility tests were conducted to ensure GA safety at tested concentrations, which is necessary after further testing to ensure it is safe to use considering this may potentially be used for diabetic wound application (2) No other biological tests conducted (e.g., fibroblast assays) to assess reaction in real-life settings, (3) Sample size was small (n=3) which reduces accuracy and limits statistical power, and lack of thermal, microscopic tests to confirm durability of material.

CONCLUSION

This research revolves around the fabrication and characterization of PVA-PEG hydrogels aimed at possible wound healing and skin rehabilitation applications. Advancements through cross-linking techniques and degradation behavior evaluation may offer new solutions to major skin injury scenarios, such as diabetic foot ulcers. To further advance this hydrogel towards clinical application, future studies should focus on performing further characterization tests, assessing in vivo biocompatibility in diabetic wound models, validating the sterilization processes to ensure clinical safety, and evaluating to what extent this can be scaled under Good Manufacturing Practices (GMP). Collaboration with clinical researchers could play a big role in enabling pilot studies in DFU patients. This will provide greater knowledge of hydrogel properties and potentially improve patient outcomes while advancing the field of rehabilitation sciences.

AUTHORS' CONTRIBUTION:

The following authors have made substantial contributions to the manuscript as under:

Conception or Design: Noor Us Sabah Motiwala, Maryam Shahab, Atika Gohar, Hiba Amer

Acquisition, Analysis, or Interpretation of Data: Amna Amin Sethi, Saima Kashif

Manuscript Writing & Approval: Noor Us Sabah Motiwala, Maryam Shahab, Atika Gohar, Hiba Amer, Amna Amin Sethi, Saima Kashif.

All authors acknowledge their accountability for all facets of the research, ensuring that any concerns regarding the accuracy or integrity of the work are duly investigated and resolved.

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REFERENCES

1. Quan T. Molecular insights of human skin epidermal and dermal aging. J Dermatol Sci. 2023;112(2):48-53.
2. Gilchrest BA. Skin aging 2003: recent advances and current concepts. Cutis. 2003;72(3 Suppl):5-10; discussion 10.
3. Chhabra S, Chhabra N, Kaur A, Gupta N. Wound healing concepts in clinical practice of OMFS. J Maxillofac Oral Surg. 2017;16(4):403-23.
4. Tiwari N, Kumar D, Priyadarshani A, et al. Recent progress in polymeric biomaterials and their potential applications in skin regeneration and wound care management. J Drug Deliv Sci Technol. 2023;82:104319.
5. Balavigneswaran CK, Selvaraj S, Vasudha TK, Iniyan S, Muthuvijayan V. Tissue engineered skin substitutes: A comprehensive review of basic design, fabrication using 3D printing, recent advances and challenges. Biomater Adv. 2023;153:213570.
6. Chen JC, Jain SA. Principles of skin grafts. In: Weinzweig J, ed. Plastic Surgery Secrets Plus. 2nd ed. Mosby; 2010. p. 677-83.
7. Imahara SD, Klein MB. Skin grafts. In: Orgill D, Blanco C, eds. Biomaterials for Treating Skin Loss. Woodhead Publishing; 2009. p. 58-79.
8. Dockery GD, Crawford ME. Lower Extremity Soft Tissue & Cutaneous Plastic Surgery. 2nd ed. Elsevier Health Sciences; 2012.
9. Chun YS, Pribaz JJ. Soft tissue reconstruction: face and neck. In: Butler CE, ed. Head and Neck Reconstruction. W.B. Saunders; 2009. p. 1-37.
10. Gaharwar AK, Singh I, Khademhosseini A. Engineered biomaterials for in situ tissue regeneration. Nat Rev Mater. 2020;5(9):686-705.
11. Norahan MH, Pedroza-González SC, Sánchez-Salazar MG, Álvarez MM, Trujillo de Santiago G. Structural and biological engineering of 3D hydrogels for wound healing. Bioact Mater. 2023;24:197-235.
12. Mundel R, Thakur T, Chatterjee M. Emerging uses of PLA–PEG copolymer in cancer drug delivery. 3 Biotech. 2022;12(2):41.
13. Li J, Ding Q, Wang H, et al. Engineering smart composite hydrogels for wearable disease monitoring. Nano-Micro Lett. 2023;15(1):105.
14. Tan HL, Kai D, Pasbakhsh P, Teow SY, Lim YY, Pushpamalar J. Electrospun cellulose acetate butyrate/polyethylene glycol (CAB/PEG) composite nanofibers: A potential scaffold for tissue engineering. Colloids Surf B Biointerfaces. 2020;188:110713.
15. Kodal M, Sirin H, Ozkoc G. Long- and short-term stability of plasticized poly(lactic acid): Effects of plasticizers type on thermal, mechanical and morphological properties. Polym Bull. 2019;76(1):423-45.
16. Beppu MM, Vieira RS, Aimoli CG, Santana CC. Crosslinking of chitosan membranes using glutaraldehyde: Effect on ion permeability and water absorption. J Membr Sci. 2007;301(1):126-30.
17. Niedzielska I, Obszyński Ł, Bąk M, Niedzielski D. The role of full-thickness skin grafts in patient's rehabilitation after maxillectomy and midface defects. J Clin Med. 2022;11(13):3608.
18. Faiz M, Imtiaz T, Zafar B, Shamim F, Khan S, Abid H. Smart foot insole for reducing the risk of foot ulcers in diabetic patients by measuring plantar pressure. Pak J Rehabil. 2024;13(1):88-98.

19. Musa BH, Hameed NJ. Effect of crosslinking agent (glutaraldehyde) on the mechanical properties of (PVA/Starch) blend and (PVA/PEG) binary blend films. J Phys Conf Ser. 2021;1795(1):012064.
20. Augustine R, Alhussain H, Zahid AA, Raza Ur Rehman S, Ahmed R, Hasan A. Crosslinking strategies to develop hydrogels for biomedical applications. In: Jose J, Thomas S, Thakur VK, eds. Nano Hydrogels: Physico-Chemical Properties and Recent Advances in Structural Designing. Springer; 2021. p. 21-57.
21. Borges FTP, Papavasiliou G, Teymour F. Characterizing the molecular architecture of hydrogels and crosslinked polymer networks beyond Flory–Rehner—I. Theory. Biomacromolecules. 2020;21(12):5104-18.
22. Reddy N, Reddy R, Jiang Q. Crosslinking biopolymers for biomedical applications. Trends Biotechnol. 2015;33(6):362-9.
23. Thumtecho S, Sriapha C, Tongpoo A, Udomsubpayakul U, Wananukul W, Trakulsrichai S. Poisoning of glutaraldehyde-containing products: Clinical characteristics and outcomes. Clin Toxicol. 2021;59(6):480-7.
24. Islam MM, AbuSamra DB, Chivu A, et al. Optimization of collagen chemical crosslinking to restore biocompatibility of tissue-engineered scaffolds. Pharmaceutics. 2021;13(6):832.
25. Liu J, Chai J, Yuan Y, et al. Dextran sulfate facilitates egg white protein to form transparent hydrogel at neutral pH: Structural, functional, and degradation properties. Food Hydrocoll. 2022;122:107094.
26. Güiza-Argüello VR, Solarte-David VA, Pinzón-Mora AV, Ávila-Quiroga JE, Becerra-Bayona SM. Current advances in the development of hydrogel-based wound dressings for diabetic foot ulcer treatment. Polymers. 2022;14(14):2764.
27. Da Silva J, Leal EC, Carvalho E, Silva EA. Innovative functional biomaterials as therapeutic wound dressings for chronic diabetic foot ulcers. Int J Mol Sci. 2023;24(12):9900.
28. Akhtar S, Ali A, Ahmad S, Khan MI, Shah S, Hassan F. The prevalence of foot ulcers in diabetic patients in Pakistan: A systematic review and meta-analysis. Front Public Health. 2022;10:1017201.
29. Sultana R, Ahmed I, Saima S, Salam MT, Sultana S. Diabetic foot ulcer: A systematic review on relevant microbial etiology and antibiotic resistance in Asian countries. Diabetes Metab Syndr. 2023;17(6):102783.
30. Rayman G, Vas P, Dhatariya K, et al. Guidelines on use of interventions to enhance healing of chronic foot ulcers in diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36 Suppl 1:e3283.
31. Sun Y, Ma L, Ji M, Wang Z. Evidence map of recommendations on diabetic foot ulcers care: A systematic review of 22 guidelines. J Tissue Viability. 2022;31(2):294-301.