**T.C.**

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**THE GRADUATE EDUCATION INSTITUTE**

**DEPARTMENT OF MOLECULAR BIOLOGY AND GENETIC**

**MOLECULAR AND MEDICAL GENETIC MASTER PROGRAM**

# MANUFACTURING AN ADVANCED SYNTHETIC GRAFT FOR GINGIVAL TISSUE ENGINEERING

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# THESIS APPROVAL PAGE

# DECLARATION

I declare that this thesis belongs to me, that I have not committed any unethical behavior at any stage, that I have obtained all the information contained in it within academic and ethical rules, that I have cited all the information I have used and included these sources in the list of sources, and that I have not committed any behavior that would violate patents and copyrights during the execution and writing of this thesis.

Reem Loai Alhalees

# DEDICATION

I dedicate this thesis to my parents, whose endless support, encouragement, and unconditional love have always guided me. I also extend my heartfelt gratitude to my dear doctor, who support me step by step to achieve the best and never let me give up.

# ACKNOWLEDGEMENT

I would like to express my appreciation to everyone who has guided me along the way as I have conducted this research and finished my thesis. Above all, I would like to express my gratitude to my supervisor, Assist Prof. Dr. İlayda DURU and Dr. Öğr. Üyesi Mustafa YILMAZ**,** whose advice and steadfast support have greatly influenced the course of this research. Their knowledge and commitment have inspired me to think critically and pursue greatness.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| **PEG** | **Polyethylene Glycol** |
| **GTA** | **Glutaraldehyde** |
| **CEJ** | **Cemento-enamel junction** |
| **JE** | **Junctional epithelial** |
| **PGA** | **Polyglycolic acid** |
| **PVA** | **Polyvinyl alcohol** |
| **PLA** | **Polylactic acid** |
| **PCL** | **Polycaprolactone** |

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# TÜRKÇE ÖZET ve ANAHTAR KELİMELER

Alhalees, R.L. (2025). Dişeti çekilmesini tedavi etmek için yumuşak doku mühendisliği tekniklerindeki son gelişmeler. Yüksek Lisans Tezi, Biruni Üniversitesi Lisansüstü Eğitim Enstitüsü, İstanbul.

Yumuşak doku mühendisliği, yara iyileşmesine katkıda bulunan ve otogreftler, allogreftler ve ksenograftlar gibi birincil yumuşak doku mühendisliği tekniklerine etkili bir alternatif olan bir hidrojel geliştirerek dişeti çekilmesini tedavi etmek için karmaşık çözümler bulmayı hedefleyen yeni yeniliklere sahip genişletilmiş bir araştırma alanıdır. Çalışma, mekanik özellikler ve bozunma oranı gibi fiziksel özellikleri artırmak için dişeti doku mühendisliğinde kullanılabilecek doğal ve sentetik polimerlerden bir greft oluşturmayı amaçlamaktadır.

Bunu yapmak için, bu tezde ayrıntılı bozunma ve mekanik analizler yürütülmüştür. Şişme testi de yapılmış ve kimyasal analizi yapmak ve hidrojel kimyasının mekanik, bozunma ve şişme sonuçlarıyla ilişkisini araştırmak için Fourier Dönüşümlü Kızılötesi Spektroskopisi (FTIR) alınmıştır. Polimerler olarak jelatin, dişeti içindeki kolajeni taklit etmek için seçilmiştir. Diş etinin mekanik dayanıklılığını artırmak için genipin ve glutaraldehit gibi farklı çapraz bağlayıcı ajanlar optimize edildi ve glutaraldehitin polietilen glikol (PEG) varlığında jelatini çapraz bağlamak için daha etkili olduğu bulundu. Ayrıca PEG'in basınç dayanıklılığını ve modülünü ve şişme/bozunma oranını da artırdığı bulundu. Doğal diş eti dokusunu simüle etmek ve esnek greftler elde etmek için Fibrin ile gelecekte araştırma yapılması gerekiyor.

**Anahtar kelimeler**: Diş Eti Çekilmesi; Jelatin – PEG Hidrojelleri; Yumusak Doku Mühendisliği.

# ENGLISH ABSTRACT and KEYWORDS

Alhalees, R.L. (2025). Recent advances in soft tissue engineering techniques for treating gingival recession. Master Thesis, Biruni University Graduate Education Institute, Istanbul.

Soft tissue engineering is an expanded research field that has new innovations that aspire to find complex solutions to treat the gingival recession by innovating a hydrogel that contribute to wound healing and be an effective alternative to the primary soft tissue engineering techniques such as autografts, allografts, and xenografts. The study aims to create a graft from natural and synthetic polymers that may be employed in gingival tissue engineering to boost the physical properties such as mechanical properties and degradation rate.

To do so, detailed degradation and mechanical analyses have been conducted in this thesis. Swelling test was also done and Fourier Transform Infrared Spectroscopy (FTIR) has been taken to do the chemical analysis and investigate the relationship of hydrogel chemistry with mechanical, degradation and swelling results. As polymers, gelatin was chosen to mimic the collagen in gingiva. To increase the mechanical strength of gingiva\ different crosslinking agents including genipin and glutaraldehyde have been optimized and glutaraldehyde (GTA) have been found more efficient for crosslinking gelatin in the presence of polyethylene glycol (PEG). It was also found that PEG increased the compressive strength and modulus and swelling/degradation rate as well. Future research with Fibrin is needed to simulate natural gingival tissue and obtain flexible grafts.

**Keyword:** Gingival Recession; Gelatin-PEG Hydrogel; Soft-Tissue Engineering.

# 1.INTRODUCTION AND PURPOSE

In the past, autografts, allografts, and xenografts have been the primary methods used in soft tissue engineering. However, because of these methods' disadvantages, including harvest-related complications and graft site morbidity, our goal is to design a graft made of natural and synthetic polymers that can be used in gingival tissue engineering to increase the physical properties of gingival scaffolds, thereby obtaining compatible materials for gingival recession.

# 2.GENERAL INFORMATION

## 2.1 Treatment of Gingival Recession

The displacement of the gingival edge apical to the cemento-enamel junction (CEJ) is known as gingival recession. It is distinguished by the simultaneous loss of alveolar bone and the loss of periodontal connective tissue fibers along the root cementum. The effective treatment for gingival recession is autograft. In an autograft, tissue is surgically removed from one area of the patient's body and transferred to another place that needs it. Though it can occasionally be taken from other places, such as the inner cheek, tissue is usually extracted from the palate in cases of gingival recession.

The procedure of autograft harvesting starts by local anesthesia then a little layer of tissue will be removed by the periodontist by making a tiny incision in the palate. Within a few weeks, the donor site will heal, and the palate tissue is often taken in a method that minimizes pain and discomfort following the process. The harvested tissue is carefully placed over the exposed tooth root and secured with small sutures (stitches). The graft is positioned so that it covers the exposed root, providing both protection and an aesthetic improvement.

Autografts have many advantages such as biocompatibility (there is no chance of rejection or allergic response) and Long-Lasting Results. Autografts are frequently successful and can produce long-lasting enhancements when done correctly. However, the donor site may experience discomfort and stress during this procedure, in addition to potential side effects include bleeding, infection, and delayed healing. Additionally, there is a limited supply of donor tissue, which might not be enough for areas experiencing a large or numerous recessions. When considerable gum tissue augmentation is required, this restriction may limit the success of autografts.

Soft tissue regeneration treatment is necessary for gingival tissue abnormalities that are most common and include gingival recession, thin gingival phenotypic, and lack of keratinized tissue surrounding natural teeth and dental implants. As of right now, the gold standard procedure that produces an elevated level of success, an ideal result, and long-term soft tissue stability is still a coronally advanced flap combined with a connective tissue graft (Adam et al., 2019; *JIAP October 2019 - Clinical Outcomes of Root Coverage with Subepithelial Connective Tissue Graft According to Site Specific Factors – Longitudinal Retrospective Clinical Study*, n.d.) .

There are certain drawbacks to this technique, though, including the need for a second surgical site to obtain the donor, which lengthens the surgical procedure and increases patient morbidity. Other complications include prolonged intra- and post-operative bleeding, infection, palate sensory impairment, and prolonged bleeding (Wang et al., 2014). Researchers worldwide are searching for alternatives to autografts due to an inadequate amount of accessible tissue for autografts. An alternative to autograft is allograft. Allograft is the donor tissue from another person.

Allografts have many advantages such as the tissue is usually easily accessible, and there is clearly no morbidity at the donor location. Large incisions are not necessary, and the procedure takes less time (Lee et al., 2019).

Allografts have disadvantaged as well such as increased nonunion rate, rapid bone resorption, infection transmission, delayed vascular penetration, and slow bone formation (Lee et al., 2019).Xenografts employ tissue from another species, typically pig or cow. Because of their affordability, reliability, comfort, and ease of use, xenografts are preferred. For the treatment of gingival recession, xenografts offer a number of benefits over autografts, but they also have disadvantages. The primary drawbacks of xenografts include their animal origin, potential for disease transmission, in vivo non-resorb ability, and ethical issues (Lee et al., 2019).

## 2.2 Gingival Tissue Engineering

### 2.2.1 Gingival Tissue

The pink, keratinized mucosa that envelops and shields the teeth is called the gingiva, or gums. The periodontium, which consists of the tooth's supporting and investing tissues, contains the gingiva. The periodontium is in charge of keeping teeth healthy and stable. Gingiva, periodontal ligament, alveolar bone, and cementum are its four constituent parts. Specialized cells called junctional epithelial (JE) cells encircle the teeth in the gingiva, sometimes referred to as the gums. Located near the base of the gingival sulcus, this junctional epithelium serves as a barrier against microbiological and mechanical insults. The lamina propria, another name

for gingival connective tissue, is made up of cells, ground material, and collagen fibers. Gingival connective tissue is composed of 60% collagen fibers and 35% ground substance, with cells making up the remaining 5%. Gingival connective tissue contains a variety of cell types, such as fibroblasts, mast cells, macrophages, and inflammatory cells. The main cell type, fibroblasts, are in charge of creating the collagen fibers and ground substance that are present in connective tissue (Brovold et al., 2018).

### 2.2.2 Scaffolds

In the past 20 years, research on gingival tissue regeneration has attempted to solve this common problem by creating and combining extremely biocompatible but delicate materials to create alternative biomaterial scaffolds that can take the place of connective tissue grafts in soft tissue regeneration (Mantha et al., 2019; Xu et al., 2017). A new field of study known as tissue engineering is described as the outcome of integrating technology from several study domains, such as biology, chemistry, engineering, medicine, pharmacy, or material science (Langer, 2000). Since tissue engineering depends on creating, refining, and optimizing three-dimensional (3D) scaffolds for tissue regeneration, repair, and healing, its significance has grown (Langer, 2000)

Recent years have seen a rapid development of tissue engineering techniques as alternate therapy for tissue abnormalities. In order to create biologically active tissues that can replace, heal, or even improve the functions of damaged tissues and organs, tissue engineering combines the knowledge of mechanical materials with cellular molecular biology (Gao et al., 2024; Li et al., 2021) Tissue engineering technology has advanced to the point where it may now be used to repair damage to a variety of tissues, including muscles, skin, gingiva, and others.

To be used as a substitute for autografts, materials for these purposes need to retain volume and exhibit favorable mechanical and biological properties for tissue regeneration. Scaffolding materials serve as the basis for tissue engineering technologies because they act as framework materials that enable cell growth into complete tissues. They also mechanically support tissue volume, release biologically active substances, and preserve tissue volume (Zamanifard et al., 2023; Zielińska et al., 2023).

Biomaterials offer a three-dimensional scaffold for cell adhesion, proliferation, and differentiation in tissue engineering. The scaffold ought to be a three-dimensional, porous structure that resembles a network and gives cells the environment they need to deposit extracellular matrix while exchanging cellular components with the surroundings. Designing biomaterial scaffolds for tissue regeneration requires careful consideration of biophysical cues, such as scaffold physical characteristics, degradation, and architectural shape, as well as

biochemical cues for utilizing natural molecules and spatiotemporal delivery of biomolecules (Carnes & Pins, 2020; Du et al., 2021) A scaffold must to be convenient to handle, preserve its shape during operation, and not impact the surrounding tissue (Mao et al., 2021).

Polymers show potential as gingival recession treatment alternatives to xenografts due to their biocompatibility, versatility, and ability to be customized for certain clinical purposes. Extremely biocompatible polymers can be created, which reduces the possibility of negative reactions or immunological reactions in patients. Specific needs, such mechanical strength, rate of degradation, and contact with adjacent tissues, can be provided with polymers. Compared to real tissue or xenografts, polymer-based materials are easier to handle and work with during surgery. In contrast to xenografts, polymers can be produced in controlled environments to ensure safety.

The use of hydrogels as a suitable scaffold for cellular migration, proliferation, differentiation, neovascularization, and biomineralization has gained interest in tissue engineering in recent years due to their unique composition and structure that mimics the natural extracellular matrix of gingiva (Ayala-Ham et al., 2021). In addition to their capacity to facilitate fibroblast proliferation, cell migration, and keratinization, hydrogels also have the advantage of absorbing exudate from the wound surface (Zhang et al., 2019). Hydrogels are also reactive as a scaffold biomaterial for tissue engineering applications, such as oral tissue regeneration, due to their shape-adaptability properties that allows simpler procedures (Ying et al., 2019).

Natural polymers provide biocompatibility, biodegradability, bioactivity, and resemblance to the extracellular matrix of natural tissues. In this regard, a number of natural polymers including collagen, gelatin, chitosan and fibrin have been tested in biomedical applications, particularly in tissue regeneration (Ansari et al., 2017; Ballios et al., 2015).

Collagen is the main constituent of the extracellular matrix (ECM) and connective tissues such as the gingiva (Brovold et al., 2018). When creating scaffolds for gingival tissue regeneration, collagen is often the first polymer taken into consideration because of its inherent abundance, biocompatibility, and resemblance to the composition of gingival tissue.

Since collagen is naturally biocompatible, the immune system does not react strongly to it. Additionally, its breakdown products are non-toxic. The mechanical and biological characteristics of collagen may be readily altered by crosslinking it or combining it with other substances. To meet particular therapeutic demands, it may be manufactured in a variety of forms. Despite its numerous benefits, collagen has several serious disadvantages that may restrict its use in the regeneration of gingival tissue. The main disadvantages are lack of bioactivity, rapid degradation rate and low mechanical strength (Lee et al., 2019).

Given these limitations, gelatin, a collagen derivative, has become a viable scaffold construction adjunct or substitute material. The hydrolysis of collagen yields gelatin, a nontoxic, biodegradable, and completely absorbable biopolymer. Gelatin has demonstrated numerous benefits over its parent protein and has been widely employed due to its biological nature, excellent solubility in aqueous systems, and inexpensive cost (Brovold et al., 2018). Gelatin has emerged as one of the naturally derived polymers that has been studied the most in the disciplines of tissue engineering and biomaterials in recent decades (Su & Wang, 2015).

Collagen can be derived from various sources to produce gelatin. The characteristics of the extracted gelatin will depend on the kind of collagen (e.g., type I, type II, and others), the age of the animal (e.g., porcine, bovine, fish), and other factors. The method used in the production process to separate gelatin from collagen affects the protein's molecular weight and isoelectric point (Gomez-Guillen et al., 2011). In order to extract gelatin from collagen, a pre-treatment is necessary to break the cross-links that keep the collagen structure stable. Alternative pre-treatments based on an acidic, alkaline, or enzymatic process are also possible.

Fibrin possesses exceptional qualities such as high biocompatibility, non-toxicity, and low immunogenicity when compared to natural materials. Furthermore, fibrin's effects on homeostasis, anti-inflammation, and wound healing distinguish it from other materials in the field of tissue engineering (Ruiz-Alonso et al., 2021). Despite their advantages, natural polymers suffer from poor processability and low mechanical strength.
In tissue engineering, scaffolds made of natural polymers have a common problem with low tensile strength, especially for applications which require durability and mechanical strength. In this context, a number of investigations have examined the drawbacks of scaffolds made of natural polymers as well as ways to enhance them, like crosslinking or blending with synthetic polymers. Some of the studies have investigated this issue such as:

**“Fabrication of Scaffolds for Bone-Tissue Regeneration” (Petra Chocholata et al. ,2019)**
This study examines the mechanical inadequacies of natural polymers including alginate, collagen, and chitosan (such as poor tensile strength and brittle behavior) that are used in scaffolds for the regeneration of both soft tissue and bone. It also examines the effects of other modification methods (such crosslinking, combining with other polymers) to enhance these natural scaffolds' mechanical qualities.

Polyglycolic acid (PGA), polyvinyl alcohol (PVA), polylactic acid (PLA), polycaprolactone (PCL) and polyethylene glycol (PEG) are extensively studied to increase the mechanical strength of natural polymers. Polyethylene glycol (PEG) melting ranges from 62 C to 65C and tends to be higher depending on the high molecular weight. The thermal degradation ranges

from 330 to 450 C. The non-isothermal degradation of PEG of Mw from 1500 to 3000 (Vrandečić et al., 2010).

Polyethylene glycol (PEG) has been investigated in a number of studies for its possible application in gingival and periodontal therapies, including the treatment of gingival recession. PEG is a biodegradable polymer that finds extensive application in tissue engineering and regenerative medicine because of its mechanical qualities, controlled degradation, and biocompatibility (Thoma et al., 2017; Zamanifard et al., 2023b).

**"Recent advancements of hydroxyapatite and polyethylene glycol (PEG) composites for tissue engineering applications – A comprehensive review"** (Zamanifard et al., 2023). The aforenmetioned study has demonstrated that PEG has potential for tissue engineering applications.

PEG has been chosen for this research due to its versatility, soft tissue-like mechanics, and non-poisoning character (Rodriguez-Rivera et al., 2024). PEG is a nontoxic FDA approved material that is utilized in many biomedical applications (Farooqui, 2018). As well as it is more cost-effective than other synthetic polymers, and its degradation period is appropriate for our experiment as opposed to other synthetic polymers that break down quickly (like PVA) or take a very long time (like PLA).

Crosslinking is a procedure for forming a 3D network structure via the formation of chemical bonds between linear molecules, enabling them to interact with one another. The crosslinking process is commonly used to increase the strength and flexibility of polymer materials. Crosslinking agents used for the study include genipin and glutaraldehyde. Genipin is a natural product derived from the Genipa americana fruit. It is biodegradable and biocompatible, and it may increase the mechanical properties of gelatin, making it helpful in wound dressing and tissue engineering (Wahba, 2024).

Glutaraldehyde is a common crosslinking agent due to its greater crosslinking efficacy when compared to other agents. It is also easily accessible, affordable in cost, and highly reactive. It has high solubility in water and organic solvents and improves the characteristics of biomaterials (Grabska-Zielińska, 2024). Based on the aforementioned ideas, the goal of this research is to successfully assist in the regeneration of periodontal tissue by creating a synthetic graft composed of natural polymers (gelatin, fibrin) and synthetic polymers (polyethylene glycol).

# 3. METHODS

## 3.1 Materials

Gelatin (Type B, from bovine skin), Glutaraldehyde (25% aqueous cross-linking agent), PEG (synthetic polymer), Phosphate buffer solution (PBS), Fibrin and Genipin.

## 3.2 Preparation of hydrogels

Manufacturing of polymeric synthetic grafts: 6 types of gelatin hydrogels were prepared.10 % of gelatin type B will be dissolved in distilled water at 60 C and 180 rpm . Gelatin solutions will be cooled at room temperature then will be combined with Polyglycolic Acid (PEG) and Glutaraldehyde (GTA) at 40 C at certain concentrations to produce a synthetic gingiva graft. The solutions were saved in room temperature for 24 hours to complete the crosslinking process. The hydrogels washed several times with distilled water to remove the unreacted chemicals.

Gelatin – Genipin solutions were prepared using 1% and 2% Gelatin dissolved in distilled water at 60 C and 180 rpm. The solutions were cooled at room temperature then different concentrations of genipin and PEG were added and stirred at 37 C and 150rpm. Some of the solutions were kept at room temperature for 48 hours and the other solutions were kept on the stirring machine for 48 hours at 37 C and 150 rpm. Different methods have been performed.

Method 1: the solutions were kept for 48 hours at room temperature

Method 2: the solutions were kept on the stirring machine for 48 hours at 37C and 150rpm.

Method 3: the solutions were kept at 37 C without stirring for 48 hours.

Method 4: the solutions were kept on the stirring machine for 48 hours at 37 C and 150 rpm then cooled at room temperature for 48 hours.

Other solutions were prepared with addition of 10 % w/v of fibrin solution. 5 gelatin solutions with different concentrations (10% - 15%) were prepared. Fibrin solution is prepared of 1g of fibrin mixed with 10 ml of PBS at 37 C. Gelatin and fibrin then mixed at 37 C until homogenous, PEG is added to all the solutions and GTA is added to some solutions. The solutions were kept for 24 hours at room temperature.

Table 1. The amounts of the components used to form the hydrogels.

| Hydrogels (5 mL) | Gelatin (w/v) | GTA (mL) | PEG (mL) |
|---|---|---|---|
| 0.25 GTA | 10% | 0.25 | - |
| 0.75 GTA | 10% | 0.75 | - |
| 0.25 GTA +0.5 PEG | 10% | 0.25 | 0.5 |
| 0.75 GTA+0.5 PEG | 10% | 0.75 | 0.5 |
| 0.25 GTA +1 PEG | 10% | 0.25 | 1 |
| 0.75 GTA +1 PEG | 10% | 0.75 | 1 |

Table 2: the amounts of the components used to prepare Gelatin – Fibrin solution

| Sample | Gelatin (% w/v) | GTA (mL) | PEG (mL) | Fibrin (10% w/v) |
|---|---|---|---|---|
| **A** | 10% | 0.75 | 1 | 0.5 ml |
| **B** | 15% | 0.75 | 1 | 0.5 ml |
| **C** | 10% | No GTA | 1 | 0.5 ml |
| **D** | 15 % | No GTA | 1 | 0.5 ml |
| **E** | 10% | No GTA | 1 | 1 ml |

Table 3: The amounts of the components used to prepare Gelatin - Genipin solutions

| Sample | Gelatin (% w/v) | Genipin (mL) | PEG (mL) |
|---|---|---|---|
| **A1** | 1% | 1 | 2 |
| **A2** | 1% | 2 | 2 |
| **A3** | 1% | 3 | 2 |
| **B1** | 2% | 1 | 2 |
| **B2** | 2% | 2 | 2 |
| **B3** | 2% | 3 | 2 |

### 3.3 FTIR Measurements

Fourier Transform Infrared Spectroscopy (FTIR): For the structural analysis of the graft, FTIR will be used to analyze the functional groups of the polymers. 32 scans will be used to record the spectrum from 4000 $cm^{-1}$ to 550 $cm^{-1}$.

### 3.4. Swelling Studies

It will be performed to determine the volume of liquid that is absorbed by the polymer, the dry polymers should be in phosphate buffered saline (PBS) for 1hour ,3 hours,5 hours,8 hours and 24 hours at 37 C. Wet samples were removed after each interval and the weights of the samples will be measured. The percentage of swelling were calculated using the equation:

$$Swelling\ (\%) = \frac{(Ww - Wd)}{(Wd)}\ 100$$

* Ww is the wet sample weight, Wd is the dried sample weight.

### 3.5DegradationTest

First, the samples will be weighted the samples will be kept in phosphate buffered saline (PBS) for 21 days, 28 days and 35 days at 37 C. Finally, the weight of the samples will be measured.

The percentage of weight loss was calculated using the equation:

$$Degradation\ (\%)\frac{(w2 - w1)}{W1}\ 100$$

*W2 is the final weight and W1 is the initial weight.

### 3.6 Mechanical Test (Compression Modulus)

For the compression test, a universal test machine which is DMA Q800 dynamic mechanic analyzer TA instrument was used. Compression test method is controlled force 2 N/min up

to 18 N. The modulus was determined using street- strain diagrams with tangential modulus method. The cross section of the samples used were 5mm* 5mm.

### 3.7 Statistical analysis

GraphPad Prism was used to analysis all of the given data. The multiple group analysis was conducted using a one-way ANOVA. All of the data's mean standard deviation was calculated. The statistical significance was determined using the p value of 0.05.

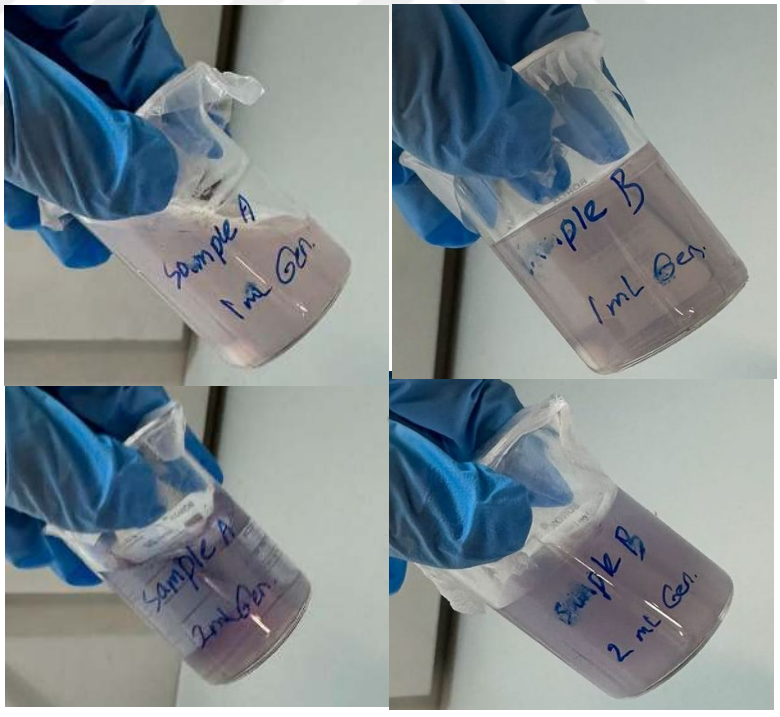
# 4. RESULTS

## 4.1 Optimization of Crosslinking

### 4.1.1 Gelatin – Genipin Solutions

The results are depending on the method of the performing the experiment. Among all the methods that were explained in the hydrogel preparation part, the best method was method 4 as all samples B show change in their viscosity based on the concentration of genipin as shown in table 3. The higher the genipin concentration in the solution, the higher the viscosity appearance. As for sample A1 and A2 they still in the liquid form and A 3 show low viscosity.

The other methods haven't affected the viscosity, only the color of the samples changed to purple. The higher the concentration of genipin in the solution, the darker the color appear. As a result, genipin hasn't considered as a good crosslinking agent as our it doesn't achieve the required viscosity of the gelatin solutions.



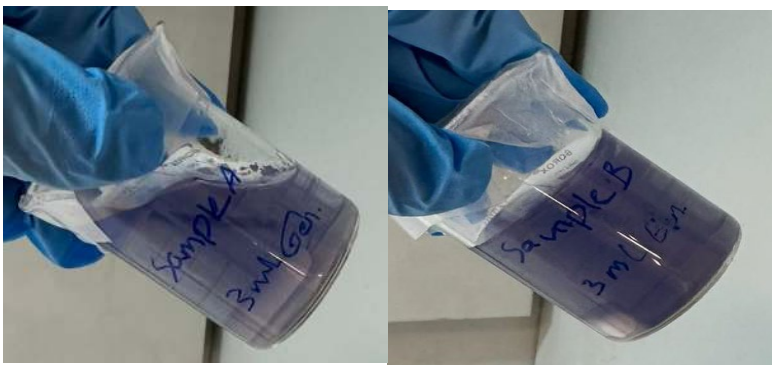



Figure 1: The results of Gelatin-Genipin solutions (A and B) after they were kept on the stirring machine for 48 hours at 37 C and 150 rpm then cooled at room temperature for 48 hours.

### 4.1.2 Gelatin-Glutaraldehyde

Glutaraldehyde has been mainly used as an effective cross-linker for the preparation of Gelatin – PEG hydrogels. Different concentration (0.25 ml and 0.75 ml) of GTA has been mixed with the hydrogels. Both used concentrations of GTA show the requested viscosity of the hydrogel. As a comparison with the previous used crosslinker (Genipin), GTA shows better and efficient crosslinking effect.

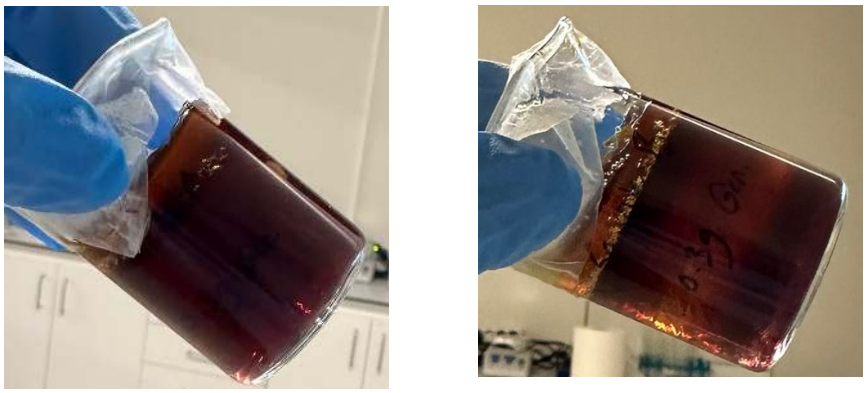


Figure 2: Gelatin- PEG solutions with 0.25 ml and 0.75 ml of GTA.

## 4.2 FTIR Test

When the GTA amount increase, the gelatin peaks disappear as shown in Figure 3. According to Figure 3, Sample 1 and sample 2 haven't shown a noticeable high peak. The FTIR spectra of the major peaks have been observed at wavenumbers of 1100 – 1180 $cm^{-1}$, 1600 -1650 $cm^{-1}$ and at 2800 $cm^{-1}$ for the samples (3-4-5-6). The peak that ranges from 1600 to 1650 $cm^{-1}$ in indicates that there is an available (C=O) stretch as well as the peak ranges

from 1100 – 1180 $cm^{-1}$ indicates the availability of C-C,C-O stretching and vibration, in the region of 1460 $cm^{-1}$ there is a $CH_2$ scissoring (Vrandečić et al., 2010).

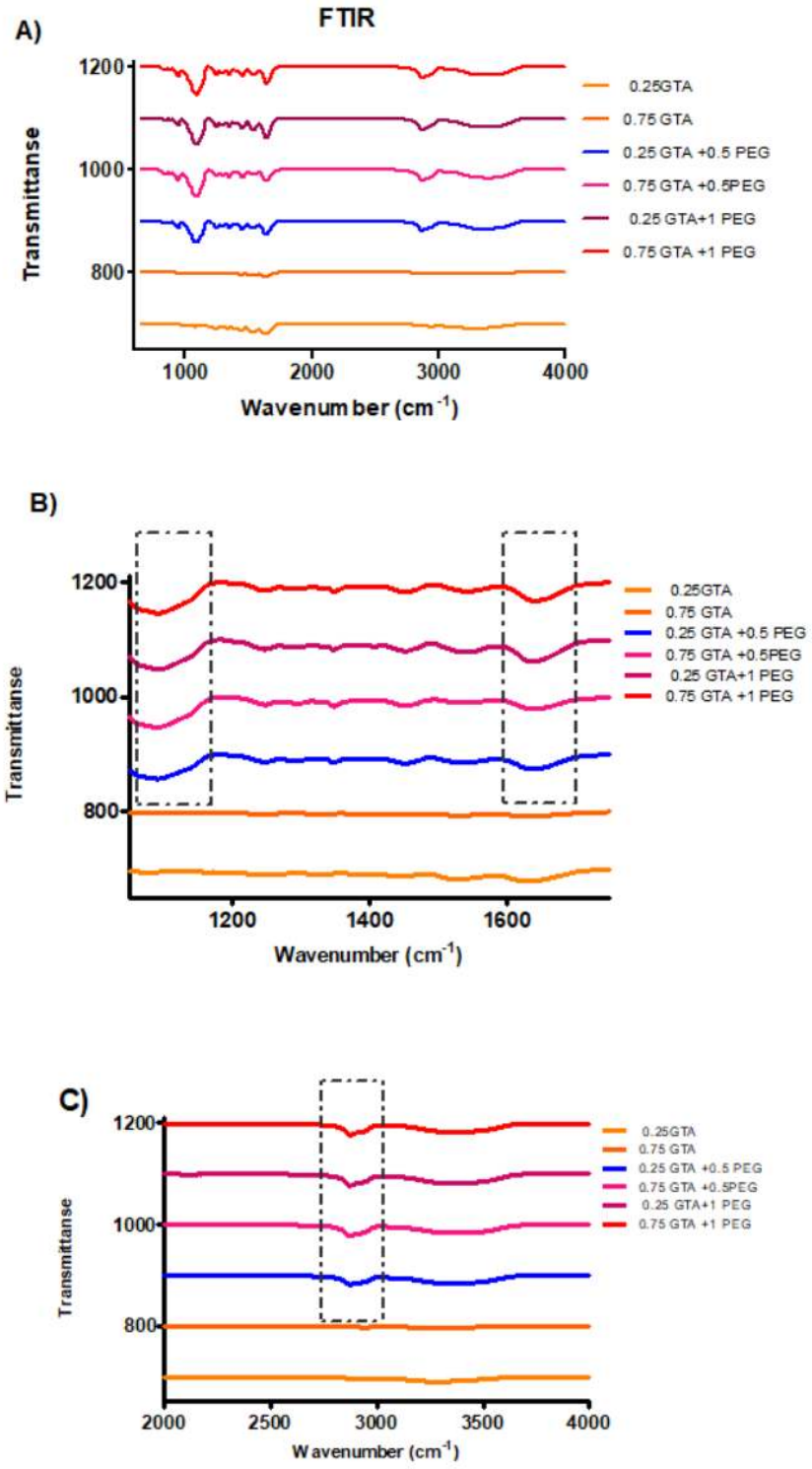



Figure 3: A) the graph demonstrates the FTIR wavelengths of the Gelatin- PEG hydrogels.

B) FTIR spectra between 1000-1180 and 1600 -1650 $cm^{-1}$.

C) FTIR spectra at 2800 $cm^{-1}$

### 4.3 SwellingTest

Figure 4 illustrates the change in swelling ratio at five distinct time points: one hour, 3 hours, 5 hours, 8 hours, and a full 24 hours for the different samples.

Sample (0.25 GTA), (0.25 GTA +0.5 PEG), (0.75GTA+0.5 PEG) (0.25GTA+1PEG) and (0.75GTA+1PEG) show swelling ranging from 10% to 50% while sample (0.75GTA) shows negative swelling about 2% at the end of first hour. In the second phase (3 hours) sample (0.25 GTA +0.5 PEG), (0.75GTA+0.5 PEG) ,(0.25GTA+1PEG) and (0.75GTA+1PEG) showed similar swelling like at the first hour, sample (0.25GTA+1PEG) swelling ratio increases to ~65%. On the other hand, sample (0.25 GTA) swelling drops off and sample (0.75GTA) negative swelling increases to -5%. As for the third phase (5 hours), variable; sample (0.25GTA+1PEG) peak reached (~70%), while other samples such as (0.25 GTA +0.5 PEG), (0.75GTA+0.5 PEG) and (0.75GTA+1PEG) decrease or exhibit minimal swelling. Sample(0.75GTA) still shows negative swelling as in the previous 2 phases. In the 8 hours swelling, sample (0.25GTA+1PEG) exhibit the largest swelling, reaching approximately 80%. In other groups, swelling reduces or remains constant. In the last phase (24 hours), no clear change in the swelling ratio for most of the samples, sample (0.25GTA+1PEG) still shows the greatest swelling among the other samples. Sample (0.25GTA and 0.75GTA) negative swelling continues, sample (0.25 GTA), (0.25 GTA +0.5 PEG) and (0.75GTA+1PEG) show stable swelling among all the hour phases.

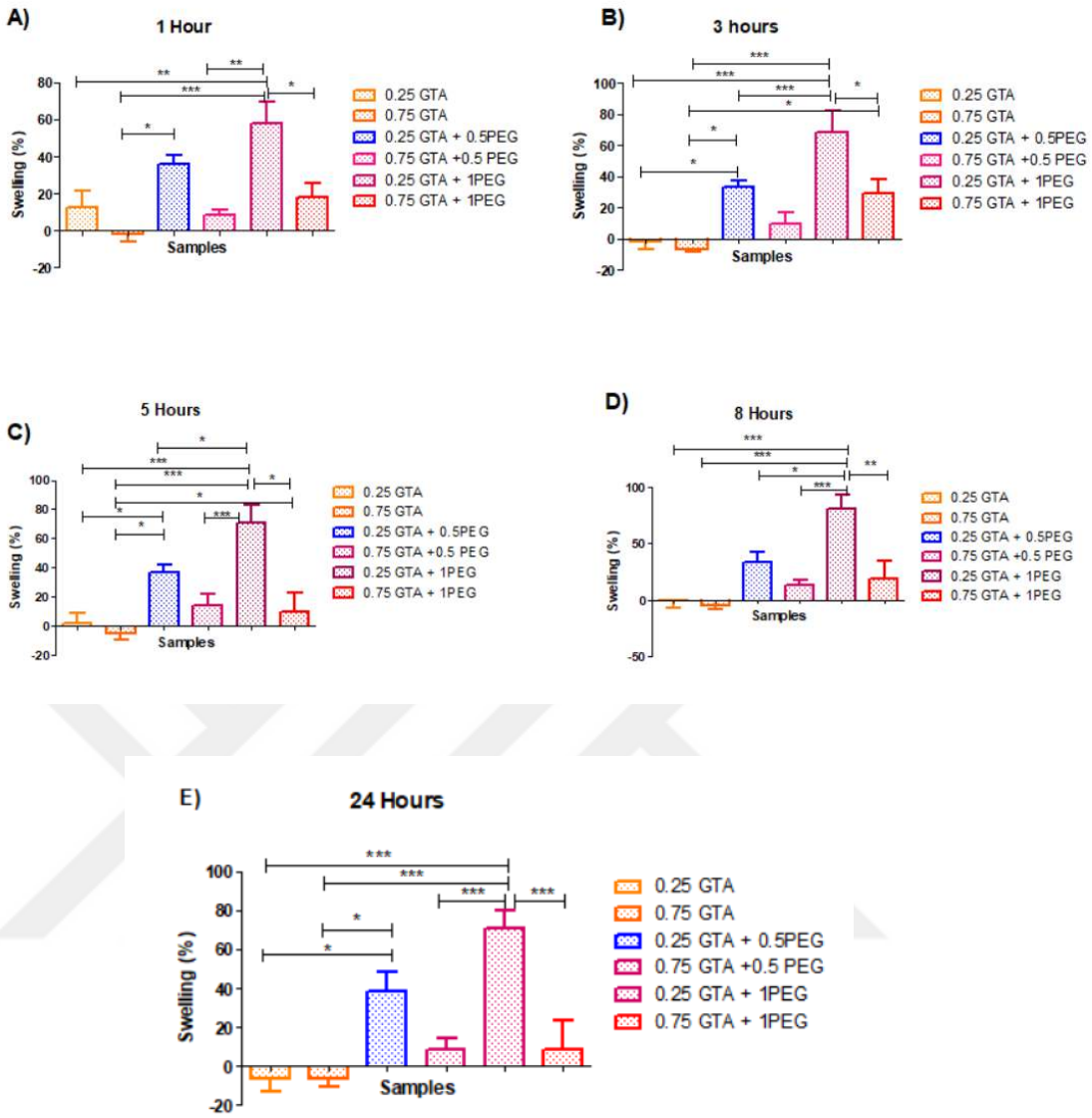



Figure 4: Swelling bar graph for the samples and the statistical significance of the swelling test.

Table 4: Best overall swelling behavior

| Rank | Sample | Comments |
|---|---|---|
| 1 | Sample3 | Balanced of swelling, stability and structure. |
| 2 | Sample 4 – Sample 6 | Maintained swelling. |
| 3 | Sample 5 | Fast swelling may affect the network stability. |
| 4 | Sample 1 | Rapid swelling then drops off – low structure stability. |
| 5 | Sample 2 | Negative swelling (not stable). |

### 4.4 Degradation Test

The degradation values of the samples vary, with some showing low and negative values (indicating that the mass of the samples increased due to swelling of the PBS). Figure 5 illustrated that sample (0.25GTA) and sample (0.75GTA) degradation ratio about 20 % in all the degradation phases (21,28 and 35 days). Sample (0.25GTA+0.5PEG) and (0.75GTA+0.5PEG) show negative degradation in first 2 phases (21 and 28 days) while it increases to about 70 % in the last phase (35 days). Sample (0.25GTA+1PEG) shows the highest negative degradation about – 50% in (21 and 28 days) while it increases to 55% in the 35 days. Sample (0.75GTA+1PEG) shows similar negative degradation to sample (0.25GTA+0.5PEG) and sample(0.75GTA+0.5PEG) in the (21, 28 days) and increase to 60 % in the 35 days.

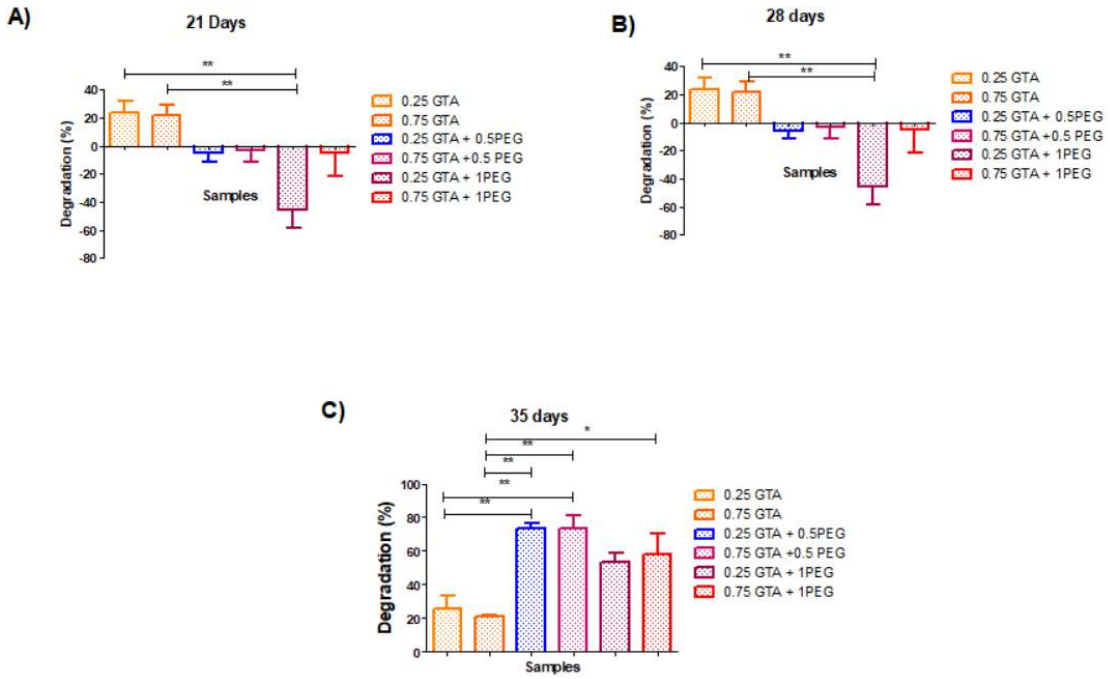



Figure 5: The graph illustrates the degradation ratio of several samples over 3 time periods.

### 4.5 Compression Test

Young's modulus E(MPa) is related to the stiffness and fracture force (N) represents mechanical strength. Stress – strain diagrams acquired from the tests and measurements of the moduli should be shown according to the results shown in table 5, sample (0.25 GTA) and sample (0.25 GTA + 1 PEG) have the highest fracture force which is around 10N and stiffness around 0.04 MPa. Sample (0.75 GTA) shows low fracture force 5.3 N and looks softer around 0.027 MPa than sample (0.25 GTA). Sample (0.25 GTA +0.5 PEG) shows balanced mechanical properties around 0.025 MPa and 7.21 N. Sample (0.75 GTA +0.5 PEG) results indicate that the sample is very soft 0.01 MPa and weak around 2.075 N. Sample (0.75 GTA + 1 PEG) is the weakest sample, it shows 0.005MPa and 1.06 N.

Table 5: Group comparison across (group 1-6) for compression test

| Group | Average E(MPa) | Average Fracture Force (N) |
|---|---|---|
| **0.25 GTA** | 0.041 | 9.345 |
| **0.75 GTA** | 0.027 | 5.305 |

| | | |
|---|---|---|
| **0.25 GTA +0.5 PEG** | 0.025 | 7.21 |
| **0.75 GTA +0.5 PEG** | 0.01 | 2.075 |
| **0.25 GTA + 1 PEG** | 0.038 | 10.815 |
| **0.75 GTA + 1 PEG** | 0.005 | 1.06 |

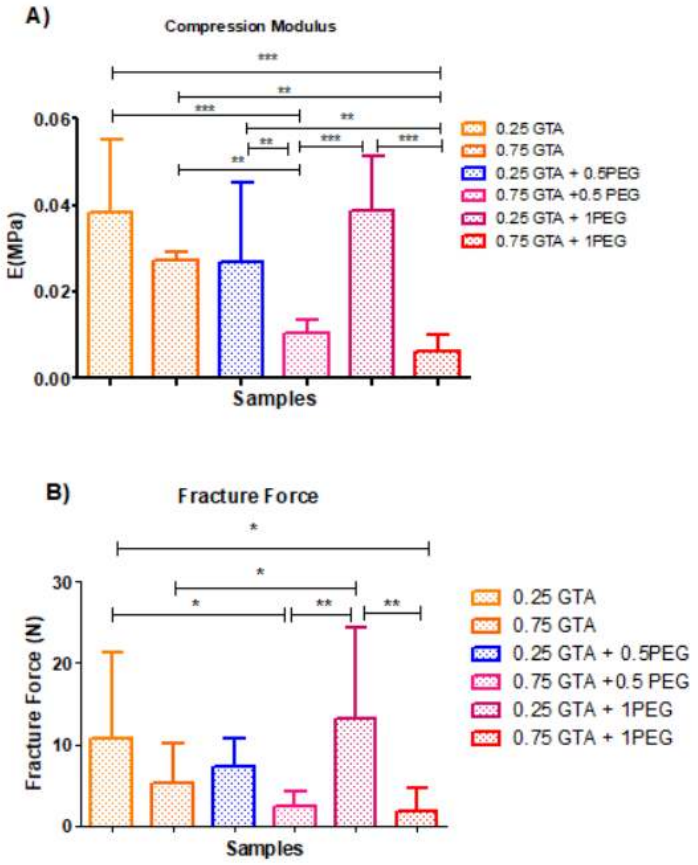



Figure 6: The graph demonstrates the statistical significance for the compression modulus and fracture force.

### 4.6 Fibrin – Gelatin Solution

According to table 2, sample A & B structure were more rigid in compare with sample C, D and E. The reason for the rigid structure is the presence of GTA in the solutions, on the other hand, the other solutions weren't 100 % solid. The solutions that contain 15 % of gelatin – fibrin have shown better stiff structure than the 10% gelatin - fibrin solution.

# 5. DISCUSSION

Based on the results, degradation and swelling have a direct relationship. Low GTA concentration (0.25ml) hasn't affected the swelling positively, as it causes noticeable water absorption in the beginning but swelling eventually decreased. Also, it shows noticeable degradation ratio and that because of the insufficient network to counter the degradation.

The increase of GTA concentration to 0.75 ml cause the hydrogel to shrink. This can happen for a number of reasons, including the fact that high glutaraldehyde creates highly crosslinked networks(Tavassoli et al., 2025), which then become extremely tight and rigid, preventing water from penetrating and creating internal tension, which results in negative swelling. In other words, there is less space to allow water absorption in a matrix that is highly crosslinked. Also, its degradation is maintained as higher crosslinking makes the hydrogel resistant to the fast degradation. The addition of PEG to the samples allows for increase the swelling as the PEG main role is forming pores enable the water absorption. The addition of 0.5 ml of PEG with low glutaraldehyde 0.25 ml adjusted the swelling behavior better than (0.25 ml) sample because PEG form pores that enable the water absorption and form a resistance action with degradation (Hutomo et al., 2023). By mixing 0.5 ml PEG with 0.75 ml of GTA, the network and hydrophilic segments become softer and lower the crosslinked regions thus the negative swelling seen in 0.75 ml is avoided. When PEG is increased to 1 ml with low glutaraldehyde (0.25 ml), the swelling and degradation increased because PEG form a lot of pores as the crosslinking network is not complicated as well as faster degradation and less structural stability due to inadequate crosslinking. High PEG and high GTA cause control and gradual swelling and degradation. As a conclusion, the sample that have high degradation will perform high swelling as well because of **polymer network structure** and **crosslinking density.**

Referred to the study conducted by Thi Xuan Quynh Nguyen et al. (Nguyen et al., 2020), The hydroxyl hydrophilic functional group found in the molecular structure of GTA enhanced the water permeability by grafting the polymer chains. The crosslinking reduced the swelling in the membrane structure by creating tightly links between the monomers to reduce the solute diffusion through the membrane.

The 0.25ml GTA considered as a sufficient crosslinking that provides balanced flexibility and structural stability or integrity and that is observed in the results shown in table 5. The high crosslinking 0.75 ml cause the sample to be rigid and brittle as well as not mechanically optimal. The hydrogels that contain low GTA with different concentrations with PEG show better mechanical properties, the high GTA with different concentrations of PEG show weak

grafts. That resulted because the low concentration of GTA enable the PEG to bind to the gelatin molecules while the high concentration of GTA bound all the functional chemical groups of gelatin which is shown in FTIR results, PEG can't bind to gelatin properly. Thus, the hydrogels with 0.25GTA and PEG show better mechanical properties than 0.75GTA and PEG.

According to results of the FTIR, the graph demonstrates 3 open bond regions which indicate that the crosslinking of the samples is in a good measurement as the higher the crosslinking value, the lower the open bond groups and as a result, high mechanical properties of the samples.

Previous study by Cebi et al. performed using different kind of gelatin extracted from different origins such as (bovine – porcine and fish) identified comparable peaks in the Amide I region that are related with C=O stretch and bending of the N-H bond with little C-N stretch. Amide III absorption is dependent on C-N stretching vibrations related to N-H bend, and Muyonga et al. suggested that the low intensity band in the Amide III area is caused by the loss of triple helix state during the gelatin extracting process (Hassan et al., 2021)

After analyzing the FTIR results illustrated in figure 3, samples that contain GTA and PEG show clear peaks in compare with samples that only contain GTA, because of the presence of PEG in the composition. PEG is a linear molecule and it forms branches that are leading to reduce the effective concentration of GTA available for crosslinking by acting as a spatial barrier leading to lower crosslinking density. As well as PEG has a functional O-H group that increases the hydrogen bonding leads to increase the hydration then increase the swelling. Moreover, when the PEG couldn't bind to gelatin/GTA molecules effectively, the samples show higher mechanical strength as shown in sample that contain low GTA and 0.5 and 1 PEG.

Combining the results of the mechanical, swelling, and degradation tests reveals that samples (0.25GTA+0.5 PEG) and sample (0.75GTA+0.5 PEG) are the most promising for the soft tissue engineering process since they closely resemble the characteristics of natural gingiva.

# 6. CONCLUSION

Gelatin is a natural polymer that is also one of the main components of the natural gingiva which encourage the idea of developing a hydrogel graft that combine the biological and mechanical properties. In this thesis, Gelatin-PEG-GTA hydrogels were created to improve the physical characteristics of gingival scaffolds, resulting in materials suitable for gingival recession.

Following an analysis of the 6 hydrogel solutions' mechanical characteristics, swelling behavior, and degradation profile, it is evident that each composition has unique benefits and drawbacks. (0.25 ml GTA + No PEG) exhibits high initial swelling and mechanical strength despite the low crosslinking. Its lack of PEG makes it less flexible and brittle over time. (0.75ml GTA+ no PEG) shows negative swelling and minimal degradation, indicating excessive crosslinking that makes it stiff but brittle.
(0.5 ml PEG) have shown balance between swlling, degradation and mechanical strength. (low GTA and 1 ml PEG) offers the best mechanical strength while maintaining degradation and fast swelling. The high crosslinking with high PEG show moderate degradation and swelling as well as it is the softest and weakest mechanically. Future work can be conducted with fibrin and human gingiva fibroblast to improve the mechanical properties and degradation rate of the gingival scaffolds.

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Manufacturing an Advanced Synthetic Graft for Gingival Tissue Engineering

**4. Araştırmanın Yapılacağı Tarih Aralığı:**

01.11.2024-01.05.2025

**5. Araştırmanın Türü:**

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# MANUFACTURING AN ADVANCED SYNTHETIC GRAFT FOR GINGIVAL TISSUE ENGINEERING

*Yazar* REEM ALHALEES

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# MANUFACTURING AN ADVANCED SYNTHETIC GRAFT FOR GINGIVAL TISSUE ENGINEERING

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