RESEARCH PAPER

To assess and evaluate the biochemical characterization of both dual crosslinking/photocrosslinking and chemical crosslinking material of Polyethylene glycol (PEG) as a material of choice for membrane adhesive

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ABSTRACT

Aim: The current study aims to develop a novel tissue adhesive based on Polyethylene glycol (PEG) as the material of choice incorporated in bisphenol A-glycidyl methacrylate (Bis-GMA)

Materials and Methods: The novel tissue adhesive was fabricated using Bis-Gma + PEG MA + Methacrylate (MA) in the ratio of 5:3:2. The tissue adhesive was then tested for biocompatibility, tensile strength, swelling test and IR test.

Results: The formed tissue adhesive exhibited swelling behavior of 0.61% and it increased to 2.07% at 3 hours. The biocompatibility of the material was 92.31% when treated against dental pulp stem cells. It also possesses tensile strength of 305.36 MPa.

Conclusion: This novel synthesized tissue adhesive may help to provide a great core for better approximation of tissues. Its increase in tensile strength over cyanoacrylates, gives a new dimension in dentistry.

Keywords: Tissue adhesive, Cyanoacrylate adhesive, Bisphenol A-glycidyl methacrylate (Bis-GMA), Polyethylene glycol

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INTRODUCTION:

Bone augmentation procedures are gaining popularity to help in osseous defects. Engineering of bone tissue and the use of scaffolds has provided a new base for multiple procedures, such as implants for bone augmentation and retrograde filling of bone in osseous defects (Schonauer et al., 2004)(Ramsundar et al., 2023; Rieshy et al., 2023; Singh et al., 2023)(Pavithra et al., 2023; Shenoy et al., 2023; Thomas & Jain, 2023). At present, Polycaprolactone has been considered for several biomedical applications, such as scaffolds for supporting fibroblasts and osteoblasts growth. It provides a hydrophobic end and is insoluble in water, but it is degradable through the hydrolytic attack of the ester bond. It has high crystallinity and hydrophilic/ hydrophobic balance between ester and methylene groups. Polycaprolactone provides long in vivo degradation times. There is a lack of bioactive functional groups and intrinsic hydrophobicity which results in poor cell adhesion, which is a critical issue for successful in vitro 3D cell culture and the subsequent tissue formation. (Rajeshkumar & Lakshmi, 2021; Sivakumar et al., 2021)

In this respect, cyanoacrylate adhesives appear to be a good choice for usage in both dentistry and medicine. The use of cyanoacrylate glue for surgical and trauma wounds was given approval by the US Food and Drug Administration in August 1998. These adhesives undergo a mildly exothermic polymerization in the

presence of the hydroxyl ions found in moist tissue. Based on the length and complexity of their chains, cyanoacrylates come in a variety of forms; they include methyl, ethyl, n-butyl, isoamyl, isohexyl, and octyl cyanoacrylates. Herod created the initial study of the use of cyanoacrylate adhesives in dentistry; however, an update is required with in vitro, in vivo, and clinical studies that incorporate new testing in conjunction with the use of commercial cyanoacrylate adhesives, which have made continuous advancements.

One of the earliest investigations on the application of cyanoacrylate glue in dental surgery was carried out by Mehta et al. The cyanoacrylate adhesive has also been employed in apicectomy, root sectioning, free gingival grafting, and bonding of broken tooth fragments. When exposed to liquids like blood or saliva, cyanoacrylate adhesives, which have good biodegradability, become rigid and have hemostatic and bacteriostatic qualities. Because of their effective hemostatic qualities and ease of use, cyanoacrylate adhesives make it possible to close oral mucosal wounds successfully. Limited gap cure, considerable reactivity that results in short shelf life, and heat generated during the curing reaction that can cause inflammation are cyanoacrylate's drawbacks.(Chokkattu et al., 2023; Dharman et al., 2023; Govindaraj & Shanmugam, 2023)). Since PEG might be employed as a preferred material for membrane adhesive in dental surgeries, this study seeks to test and evaluate the biochemical characterization of both dual cross linking/photo crosslinking and chemical crosslinking material of PEG.

Polyethylene Glycol (PEG) has been used earlier as a bone wax. Bone wax is a sterile beeswax softened with isopropyl palmitate or paraffin that is used as bone hemostatic during surgery involving bone dissection by occluding the blood channels mechanically after being smeared over the cutting area. Although bone wax is very effective in controlling local bone bleeding, the drawback of widely used bone wax is that it is not resorbable.(Gandhi et al., 2021; Katyal et al., 2023; Priyadharshini et al., 2023)The concluded studies have lacunas regarding the strength of cyanoacrylates. The highest provided level of strength is 150 MPa which can be achieved by cyanoacrylates and that cannot provide acceptable results in bone adhesion. The novel architecture of using PEG might help overcome this lacuna. Depending on its molecular weight, PEG is also known as polyethylene oxide (PEO) or polyoxyethylene (POE). H(O)CH2CH2nOH is a popular way to express the structure of PEG(Doshi et al., 2023; Lampl et al., 2023; Pandiyan et al., 2023). The synthetic polymer poly (ethylene glycol, or PEG), which is hydrophilic and biocompatible, is widely used in biomedical and other applications. PEGs are extensively employed in a variety of biomedical applications, such as bioconjugation, drug administration, and tissue engineering. They are non-toxic, FDA-approved, and often non-immunogenic(Janani et al., 2021; Kachhara et al., 2021; Subramanian et al., 2023). If proven right the combination of PEG might help in adhesion with the bone and provide better mechanical strength and ease of use for the practitioner.

This study deals with evaluation and biomechanical characterization of both dual cure crosslinking/ photo crosslinking and chemical crosslinking material of PEG as a material of choice for membrane adhesive. (Rajeshkumar & Lakshmi, 2021; Sivakumar et al., 2021)

MATERIALS & METHODS:

1. **FABRICATION OF TISSUE ADHESIVE MATERIAL:**

   The adhesive material was fabricated by mixing 50 wt.% Bis-GMA to PEG and methacrylic acid of ratio 3:2. 1% Hyaluronic acid was added as filler material and the solution was stirred to form a homogenous solution. 100 µl of 0.5% Irgacure 2959 was added as a photo initiator. The solution was exposed to UV radiation (365 nm) for 10 mins. The material was stored at room temperature for further analysis.

2. **ATTENUATED TOTAL REFLECTANCE FOURIER TRANSFORM INFRARED SPECTROSCOPY (ATR-FTIR):**

   Attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) is a powerful technique to determine any possible chemical interaction ATR-FTIR spectroscopic analysis was performed using Bruker ATR infrared spectrometer. The functionalities of the Bis-GMA and GelMA was confirmed by the FTIR spectrum.

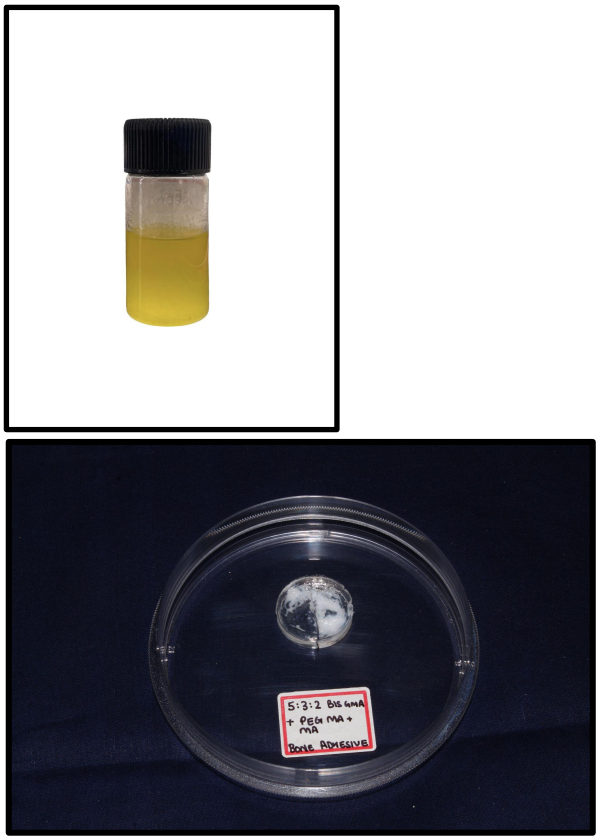


Figure 1: Fabrication of Tissue adhesive

MECHANICAL TESTING:

1. **SWELLING RATIO (%) OF THE FABRICATED MATERIAL**

The swelling behavior of the adhesive material was studied by immersing 10mg of the material in 500 µl of artificial saliva. After 1 hr, the material was removed from the artificial saliva, dabbed to remove excess solution, weighed and placed back into the solution. The similar process was performed after 3 hr. The swelling ratio (%) were calculated using the following equation.

Swelling ratio (SR) = $((W_w - W_0)/W_0) \times 100\%$

W_0 and W_w are the initial dry weight and the wet weight, respectively.

2. **DEGRADATION BEHAVIOUR (%) OF THE FABRICATED MATERIAL**

The degradation of the material was conducted to analyze the weight loss of the material over a period. 10mg of the fabricated material was immersed in 500 µl artificial saliva. The material was taken out dried and weighed during the predetermined time points. The percentage of the degradation was determined for 28 days. The % degradation were calculated using the following equation.

% Degradation = $((W_0 - W_t)/W_0) \times 100\%$

W_0 and W_t are the initial dry weight and weight after incubation at a time ‘‘t”, respectively.

3. **DENTAL PULP STEM CELLS (HDPSC) CELL CULTURE**

After obtaining informed consent and ethical approval from SIMATS ethics committee, the Dental Pulp stem cells were isolated from molars. The cells were cultured in DMEM-F12 / 10% FBS / 1% Penicillin-streptomycin. After two passages, the cells were used for cell viability and compatibility assays.

4. **BIOCOMPATIBILITY ANALYSIS**

10 mg of sample was prepared, and UV treated. 1000 cells per well were seeded in 48 well plates and treated with DMEM-F12 /1% Penicillin-streptomycin media. The prepared sample was placed onto the media. After 24hrs of culture, 10uL/100mL of MTT reagent (5 mg/mL stock) was added to cultured cells and then incubated for 4 h to allow the formation of the formazan dye at 37℃. The medium is exchanged to DMSO (200 µL) and stands for 10min. The reaction product was transferred to a 96 well ELISA plate and A590 was measured with ELISA plate reader.

STATISTICAL ANALYSIS:

All values are expressed as the mean ± standard error of the mean (SEM) of at least three independent experiments. A one-way ANOVA (analysis of variance) was used to test for significant differences, and multiple comparisons were performed using Scheffe’s method. Statistical significance was set at $p<0.05$.

RESULTS:

1. **FTIR Test:**

The Fourier Transform Infrared (FTIR) spectra of Bis-GMA, PEGDA, and their combination (Bis-GMA + PEGDA) demonstrated distinct functional group characteristics and confirmed interaction between the components.

The Bis-GMA spectrum showed characteristic absorption bands corresponding to hydroxyl (–OH) stretching around 3400–3500 cm^{-1}, indicating hydrogen bonding within the resin matrix. A prominent peak near 1720 cm^{-1} was attributed to carbonyl (C=O) stretching, while bands in the region of 1600–1500 cm^{-1} corresponded to aromatic C=C

stretching. Strong absorption peaks in the 1100–1000 cm^{-1} range were associated with C–O–C stretching vibrations, confirming the presence of ether linkages.

The PEGDA spectrum exhibited a comparatively simpler profile with a distinct peak around 1720 cm^{-1} corresponding to ester carbonyl (C=O) groups. Peaks in the 1100–1150 cm^{-1} region were assigned to C–O stretching of ester linkages. The absence of a broad hydroxyl peak indicated lower hydrogen bonding potential compared to Bis-GMA.

In the combined Bis-GMA + PEGDA spectrum, the major peaks of both individual components were retained, confirming successful incorporation. Minor shifts and variations in peak intensities were observed, particularly in the carbonyl (approximately 1720 cm^{-1}) and ether (1000–1100 cm^{-1}) regions, suggesting intermolecular interactions and possible copolymerization. A reduction in the intensity of certain peaks further indicated consumption of reactive functional groups during polymer network formation.

Overall, the FTIR results indicate chemical compatibility between Bis-GMA and PEGDA, with preservation of key functional groups and evidence of structural integration within the composite.

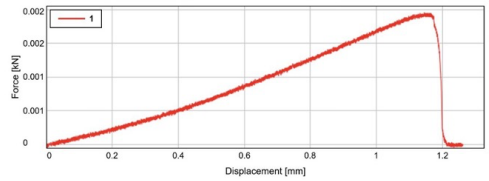
2. Compressive strength :

The tensile testing of the specimen (5:3:2 Bis-GMA + PEGMA + MA) demonstrated a typical stress–strain behavior with an initial linear elastic region followed by failure. The force–displacement curve showed a steady increase in force with increasing displacement, indicating uniform load-bearing capacity up to fracture.

The specimen exhibited a maximum force of 1.95 N, corresponding to a tensile strength of 305.36 MPa**.** The material sustained deformation up to a displacement of approximately 1.2 mm, beyond which a sudden drop in force was observed, indicating brittle fracture behavior.

The tensile strain at break was calculated as 2.52%**,** suggesting limited ductility of the material. Additionally, the tensile stress at break was recorded as 1.00 MPa (standard value)**,** confirming that failure occurred abruptly after reaching peak stress without significant plastic deformation.

Overall, the material demonstrated high tensile strength with low elongation, indicating a predominantly brittle mechanical response suitable for applications requiring rigidity and strength rather than flexibility.



	Maximum Force [N]	Tensile stress at Tensile strength [MPa]	Tensile strain (Displacement) at Break (Standard) [%]
1	1.95	305.36	2.52

	Specimen label	Tensile stress at Break (Standard) [MPa]
1	5:3:2 Bis GMA + PEGMA + MA	1.00

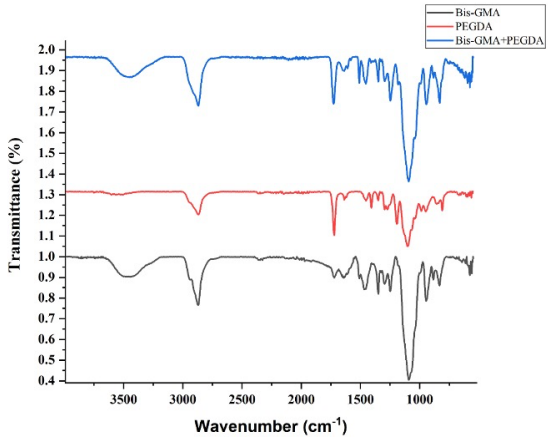


Figure 5 - Compressive strength of fabricated Bone Adhesive Material

3. Swelling test :

The absorption of body fluid and the transfer of cells, nutrients and metabolites are influenced by the swelling behavior of the scaffold. The swelling of the material in the fluid results in the increase of the pore size, total porosity and maximize the internal surface area of the scaffold. It aids in the infiltration of cells in the scaffold. However, if the swelling is higher, it would negatively affect the mechanical properties of the scaffold. All the synthesized scaffolds showed swelling behavior of which is ideal for cell infiltration and nutrient flow. During tissue engineering, the degradation of scaffolds plays an important role. The

scaffolds must degrade at a rate proportional to that of the bone formation. The fast degradation of the scaffold leads to scaffold collapse and may result in tissue necrosis. The degradation profile of the fabricated scaffold was analyzed over 14 days. All the fabricated scaffolds showed less than 50% degradation over 14 days.

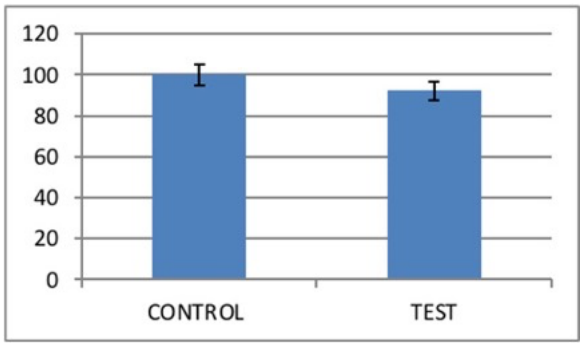


Figure 6 - Swelling test of tissue adhesive

4. **Bio-compatibility test :**

The comparative analysis between the control and test groups demonstrated a reduction in the measured parameter in the test group. The control group exhibited a mean value of approximately 100 units, whereas the test group showed a lower mean value of approximately 92 units.

Error bars representing standard deviation indicated minimal variability within both groups, suggesting consistency in the measurements. Although the test group showed a decrease in mean value compared to the control, the overlap of error bars suggests that the difference may not be statistically significant.

Overall, the findings indicate a slight reduction in the evaluated parameter in the test group when compared to the control group, with relatively low dispersion of data in both groups.

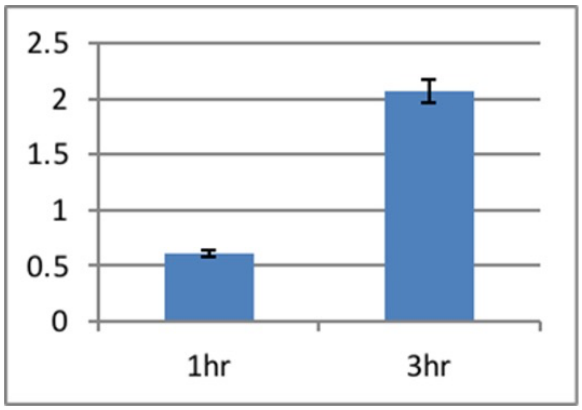


Figure 7 - Biocompatibility of fabricated material against dental pulp stem cells

DISCUSSION:

There are several ideal properties that would generally be expected for a tissue adhesive developed for wound healing: both the tissue adhesive and its degradation products should be compatible with tissues. Therefore, researchers are confronted with the challenge of developing a reactive monomer that provides rapid polymerization and using biocompatible initiators. The tissue adhesive should adhere to a wet or moisture surface at approximately body temperature. Furthermore, surgical tissue adhesives should provide proper applying time, biodegradability, strong and flexible bonding, spreading capacity and wettability. Thus, PEG is reviewed as a newer material for tissue adhesive in this article. Polyethylene glycols (PEGs) are products of condensed ethylene oxide and water that can have various derivatives and functions. Since many PEG types are hydrophilic, they are favorably used as penetration enhancers. Most PEGs are commonly available commercially as mixtures of different oligomer sizes in broadly- or narrowly defined molecular weight (MW) ranges.

In PEG and dopamine hydrogel, the peaks of 1000–1150 cm−1, 2880 cm−1 and 1729 cm−1 assign to the ether, alkyl and carbonyl functional groups in PEG–dopamine chemical interaction, which is an indicating of crosslinking.95 1H nuclear magnetic resonance spectroscopy (1H NMR) and ultraviolet-visible (UV) spectrophotometer analysis have also been employed to characterize the structure.

Barret *et al.* developed mussel protein based amphiphilic poly (propylene oxide) (PPO)-poly

(ethylene oxide) (PEO) polymer hydrogels that can be formed *in situ* for surgical wound treatment. The hydrogel demonstrated stresses of 3.4-4.3 MPa and 90% strain without any rupture and damage. Also, Liu *et al.* modified and improved adhesion and bio interaction properties of PEG based tissue adhesive by applying dopamine, catechol groups and nanoparticles. Studies showed that the strength of lap-joint enhances when the bond line becomes thinner, thickness minimizes or in tough adhesives. The highest strength was obtained for bond lines in the range of 0.05 to 0.5 mm. The adhesive strength may also be affected by other parameters, such as the type of loading including shear, peel, or cleavage, the adherent elastic or plastic behavior, and the adhesive ductility or brittleness.

As to the characterization of biocompatibility, primary *in vitro* tests like the methlythiazoletetrazolium (MTT) assay, hemostasis analysis and histological analysis provide functionality and biocompatibility evaluations. The viability of cells exposed to the tissue adhesive samples determines cytotoxicity, with cell viability less than 70% being considered as non-biocompatible adhesives. (2)

Modifications of the physico-chemical properties of PEG hydrogels and the addition of arginine–glycine–aspartic acid (RGD) influenced soft and hard tissue integration and biodegradation. A dense network PEG hydrogel showed an increased degradation time and maintained the shape. The soft tissue integration was enhanced by adding an RGD sequence. A high turn-over rate and extensive bone regeneration was observed using loose network of PEG hydrogel. The addition of RGD further improved bone formation and soft tissue integration. (1)

Suturing is the most common method to achieve tissue approximation and wound healing in dentistry. Sutures can provide great tensile strength and show relatively low failure rate. Suture materials can be grossly divided in biologic or synthetic and in absorbable or non-absorbable. Nylon was the first synthetic suture applied and is still the most widely used non-absorbable suture. Disadvantages are the need to remove the suture provoking high stress concentration at the suture point and the granuloma formation when it resides long in the body. Absorbable sutures, however, frequently evoke inflammatory reactions and are relatively expensive. A common feature of suturing is the inevitable penetration of surrounding tissue, nerve damage and post-surgical adhesion which can occur and the ischemia and necrosis of entrapped tissue caused by damaged capillaries. Needle holes and necrotic spaces might provide a passage for fluids or air to leak out. Such compromised tissue anastomosis may result in severe complications depending on the leaking material. Thus, the future scope of this study is the fabrication of a novel tissue adhesive which can help in a better approximation of the tissues with minimally invasive technique and at a faster time than conventional suturing techniques.

Despite of the benefits and advantages of tissue adhesives discussed in this review, dopamine based tissue adhesives do show some limitations including low mechanical strength under loading in hard tissues repair, poor adhesion in highly wet environment in which co-closure with suture has been required. It is still a challenge to develop a perfect bioadhesive that can adhere to tissues and stop bleeding completely, be biocompatible, non-toxic and biodegradable, be cost effective and simple to use in order to attract surgeons for applications in complicated surgical situations. Furthermore, the synthetic techniques are complex for the majority of mussel inspired tissue adhesives.152 Several strategies have been done in recent years to face the current demands in tissue gluing; however, more characterizations and different side effects assessment in short or long terms use are needed.

The advent of different wound closure methods has provided promising alternatives for such traditional wound closure methods as suturing. The knot tying procedure for sutures may cause tissue distortion, residual force, blocking of blood perfusion, and consequently impede wound healing. Foreign body reaction is another adverse outcome of sutures, especially at a site of knotting which represents a major mass of foreign body. A primary closure of wounds, suturing sometimes may not be feasible because of the inadequacy of the skin flaps, especially after trauma or following excision of lesions. In this regard, alternative methods for surgical wound closure such as biological glues and tissue adhesives have gained more attentions recently. Tissue adhesives offer various advantages over traditional wound

closure methods include easiness to apply, causing less pain and no need for removal in a further visit.

The choice between dual crosslinking/photo crosslinking and chemical crosslinking depends on the specific requirements of the application. Surgical procedures may benefit from the spatial and temporal control offered by dual crosslinking, while simpler applications might favor the cost-effectiveness of chemical crosslinking. Biocompatibility is a critical consideration for membrane adhesives. Both methods should be thoroughly evaluated for their impact on tissue biocompatibility and long-term performance. Further research is needed to assess the long-term stability and degradation characteristics of both adhesive methods to ensure their suitability for various medical and pharmaceutical applications. The choice of crosslinking method may also depend on the scale of production. Large-scale manufacturing may favor chemical crosslinking due to its simplicity and cost-effectiveness.

PEG is used as tissue adhesive for corneal incision closure following Descemet membrane endothelial keratoplasty. This study contributes to the literature of suture less closure of corneal incisions. As the PEG-closed incisions did not experience any leakage and allowed sufficient wound healing to prevent the wound reopening during rebubbling, we conclude that PEG should be considered as an alternative to sutures. To investigate degradation of our protein-PEG hydrogels by proteolysis, we employed the volume-change method as previously utilized by Lutolf et al. for similar hydrogel systems. The degradation characteristics of hydrogels correlated directly with the properties of each hydrogel's protein polymer constituent in soluble form. For instance, hydrogels formed from degradable protein constructs and incubated with MMP-1 or plasmin started to swell due to bulk enzymatic degradation until collapsing. In contrast, no degradation was observed using this method in the case of hydrogels formed from nondegradable protein constructs that were exposed to MMP-1. Nondegradable gels remained unaffected by MMP-1 as manifest in constant gel volumes during incubation with protease. However, slow swelling of presumed nondegradable matrixes was measurable in response to plasmin, in agreement with the finding that unexpected sites in the protein polymers were susceptible to slow degradation by plasmin, namely the RGD cell-adhesion site present in all constructs. The degradation rate of nondegradable matrixes during plasmin exposure was significantly slower compared to that of degradable matrixes. Furthermore, the swelling rate of nondegradable hydrogels tended to slow during plasmin incubation. This was probably due to loss of enzyme activity after long incubation periods (presumably caused by autoproteolysis of enzyme). Ultimately, nondegradable hydrogels remained intact for several weeks. Upon exposure to proteases, the observed volume increase of the degradable hydrogels indicates a predominance of bulk over surface degradation of the network. This implies that proteases reached homogeneous distribution within the hydrogels during network degradation. According to Lutolf et al., in the case of the MMP-1 degradation studies the concentrations of the protease (5 nM) and of the corresponding GPQGVIAGQ-substrate (2.43 mM and 3.63 mM for the degradable dimer and tetramer, respectively) were within a range to result in a zero-order rate of hydrolysis, i.e., with the enzyme being fully saturated with substrate. Taken together, these findings show conclusively that the sensitivity of hybrid-hydrogels to specific proteolytic degradation can be controlled through the rational design of chemically and genetically engineered biological components. Hydrogels Promote Cell Adhesion. The fibrin-derived RGD site incorporated in our protein constructs, which was intended to produce the cell-binding properties of our protein polymers, was also used by Halstenberg et al. to effect cell adhesion to a similar recombinant protein polymer. An increase in cell adhesion to coated tissue-culture polystyrene (TCPS) was observed when increasing the concentration of adsorbed protein polymers on the surface. Cell adhesion was inhibited by increasing the medium concentration of a soluble competing integrin ligand, namely the cyclic RGD-peptide, cyclic-RGDFV. Moreover, the protein polymer containing the mutated RGD site, namely RGG, did not support cell adhesion, indicating the specificity of cellular interactions via integrin receptors with the RGD site that was present in the protein polymers.

CONCLUSION:

The biochemical characterization of dual crosslinking/photo crosslinking and chemical

crosslinking of Polyethylene Glycol (PEG) for membrane adhesive applications presents distinct advantages and challenges. Careful consideration of the specific requirements of each application, biocompatibility, and long-term stability is essential in choosing the appropriate method. Further research in this field will contribute to the development of effective and safe membrane adhesives for a wide range of biomedical applications.

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