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# Development of Injectable Biodegradable Multi-Arms PEG-Based Hydrogels: Swelling and Degradation Investigations

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**Summary**: Injectable biodegradable hydrogels have been developed to determine the efficacy of biomaterials for the treatment of periodontitis through control delivery of bone-healing bioactives. The hydrogels were prepared from the PEG-ylated macromer of Boltron$^{TM}$ H20 (BH20) and an acrylated triblock copolymer of polylactide-polyethylene glycol (2k)-polylactide (PLA) in various molar ratios using ammonium persulfate and sodium ascorbate as a free radical initiating system. Preliminary investigations involving the synthesis of PLA hydrogels with different PLLA block lengths were studied in order to determine the swelling ratios and degradation rates of the biodegradable component of the hydrogels prior to copolymerization with BH20. The swelling and degradation studies of PLA with PEG diacrylate (FW 700) hydrogels were established in phosphate buffered saline (PBS) at 37 °C, pH 7.4 and in water (pH ~5.5). They have been shown to have low swelling ratios ($Q_{max} = 4.4$ to 3.6) and degradation times of 20–30 days. The swelling and degradation parameters were found to be dependent on the molar ratio of the PEG diacrylate to PLA in the copolymer.

**Keywords:** degradation; hydrogels; multi-arms macromers; structure-property relations; swelling

## Introduction

Periodontitis or inflammatory gum diseases are caused by a convergence of bacteria that adhere to and grow on the tooth surface below the gum line. It affects 40–50% of the population above 30 years old and progressively leads to the irreversible loss of the alveolar bone around the teeth.[1] Dental implants are an ideal option for people who suffer from periodontitis, to improve their dental aesthetics and function.

Implant-based dental reconstruction is the fastest growing segment of the dental market with a forecast growth rate of almost 15% and a worldwide market approaching US $3.5 billion by 2010.[1] However, the market for treating dental diseases, including periodontitis, through improvement of bonding between jawbone and teeth is expected to exceed the above figure by several-fold. Generally, dental implants enjoy a reasonable success rate if case selection is optimised. However, clinical success rate can vary from patient to patient, depending on their general health. A failure rate due to peri-implantitis of 10–15% for dental implants has been reported.[2]

The principal goal for this work is to develop an effective method for the treatment of periodontitis and peri-implantitis through controlled delivery of bone-healing

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bioactives from biodegradable hydrogels. Recently, we found that LipoxinA4 anti-inflammatory agent encourages bone healing if administered regularly to the infected site over an extended period of time.[3] In this study, we report the synthesis and characterization of a series of multi-functional biodegradable hydrogels that can be cured *in-situ* in conjunction with growth factors and LipoxinA4 as conjugates or simply encapsulated, in order to determine the efficacy of these biomaterials for the treatment of periodontitis through control delivery of bone-healing bioactives. Furthermore, it is worth mentioning that the high swelling ratios would compromise the integrity of the dental implant, therefore low swelling values for these hydrogels are required. Similarly, the drug release from these hydrogels is directly related to their rate of degradation.

## Results and Discussion

Hydrogels based on PLLA have been recognized to be suitable vehicles for the delivery of bioactive molecules, due to their useful physical and chemical properties. PLLA-*b*-PEG-*b*-PLLA (PLA) macromers were designed to maintain all of the advantages of a PEG-based material while permitting tuneable degradability. As the utilization of PLA gels has increased, this characteristic of tuneable degradability has become extremely useful in the biomedical field. It has been used to eliminate the need for physical removal of PLLA implants, as well as to modulate the delivery rates of drugs or the growth rates of cells encapsulated within cross-linked PLA matrices.

Initial results from this study show that hydrogels with short blocks of PLLA (3–4 units) are more suitable for the intended application, because longer PLLA blocks compromise the solubility of the macromers in water prior to their crosslinking, which is a prerequisite for their application. Therefore in this study triblock macromers of PLLA-*b*-PEG-*b*-PLLA (PLA) with 3-4 PLLA units were used in the synthesis of the hydrogels. A series of hydrogels based on PLA copolymerized with different molar ratios of PEG diacrylate-FW = 700 (PEGDA) were synthesised with the aim to determine the swelling ratios and degradation rates of the biodegradable component of the hydrogels, prior to their copolymerization with acrylated multi-arm Boltorn H20 (BH20). Table 1 shows the hydrogel swelling ratios at equilibrium in phosphate buffered saline solution (PBS-pH = 7.4) as a function of the PEGDA to PLA ratio. By incorporating higher PEGDA the crosslink density increases, hence lower swelling ratios were observed. However, at higher PEGDA (PEG20:PLA80), an increase in the swelling ratio was observed, which can be attributed to the increase in the hydrogel hydrophilicity. From the swelling study, PLA100 hydrogel was selected for the degradation study, and was predicted to degrade faster than the gels with PEGDA. This prediction was based on the higher swelling ratio of PLA100 compared to the other hydrogels, since higher water contents lead to faster hydrolysis of the PLLA ester bonds, and therefore faster matrix degradation rates.

***Table 1.***
Hydrogel compositions and equilibrium swelling ratios of PEGDA/PLLA-PEG-PLLA in PBS at pH 7.4 (37 °C).

| Hydrogel Code | Hydrogel Compositions Weight Fraction | | Hydrogel Property |
|---|---|---|---|
| | PEG; Poly(ethylene) glycol diacrylate (FW = 700) | PLA; diacrylated PLLA-PEG-PLLA (3:45:4) | Swelling Ratio |
| PLA100 | 0 | 1 | 4.4 |
| PEG5:PLA95 | 0.05 | 0.95 | 4.2 |
| PEG10:PLA90 | 0.10 | 0.90 | 3.8 |
| PEG15:PLA85 | 0.15 | 0.85 | 3.6 |
| PEG20:PLA80 | 0.20 | 0.80 | 4.1 |

According to previously developed degradation models of PLA-*b*-PEG-*b*-PLA based hydrogels, there are two main parameters that affect the form and rate of network degradation. The first is the hydrolysis kinetics of the PLA ester bonds within the cross-linked hydrogel. The second is the physical structure of the gels. These two parameters are interdependent, making the entire gel degradation process very complex. It has been reported recently that increasing the molecular weight of the PEG segment decreases the crosslink density (structural effect), which in turn increases the water content of PLA-*b*-PEG-*b*-PLA gels.[4,5] This leads to an increase in the rate of hydrolysis of PLA ester bonds (kinetic effect) and therefore the overall gel matrix degradation rate. The ability to tailor hydrogel crosslink density can also be used to control network mesh size and diffusivities of encapsulated drugs. Anseth et al.[6] have shown that the initial mesh size of the hydrogel network, as well as the matrix degradation rate, affect the drug release profile. Faster degradation rates result in faster increases in mesh size, and thus more rapid drug release.

The degradation profile of PLA100 was investigated at two pH values (5.5 and 7.4). It has been reported that the rate of hydrolysis of the ester bonds of PLLA is higher at pHs both higher and lower than the lactic acid pKa value (pKa = 3).[4] So, the rate constant for ester hydrolysis will be greater at the higher pH value of 7.4. Figure 1 is plot of Mt/Meq with time (Mt is mass of swollen hydrogel at time ‘‘t’’, while Meq is the mass at equilibrium swelling). The increase in Mt/Meq indicates higher swelling ratio which is due to a decrease in crosslink density of the hydrogel as it degrades. This figure shows that the hydrogel degraded completely at day 20 in PBS buffer (pH 7.4 at 37 °C) as a result of the catalysed hydrolysis of the ester bonds in the PLA component. By contrast, the hydrogel showed a very slow rate of degradation in water at pH 5.5. This can be attributed to two factors. Firstly, the pH is lower than for the PBS solution, and secondly the water is unbuffered, so as the lactic acid hydrolysis product is formed, the pH of the solution will drop below 5.5, so decreasing the hydrolysis rate. At pHs in the proximity of the pKa of lactic acid (pKa = 3), ester bonds remain mostly unbroken over 20 days, hence at pH = 5.5 the hydrogel only swelled to an equilibrium after 20 days.

The effect of the multi-arm macromer (BH20) on hydrogel morphology and swelling ratios has also been studied (see Figure 2). The results showed that hydrogels with high molar ratios of BH20 macromer produce highly porous morphologies when compared to gels with lower contents of BH20. Furthermore, BH20-

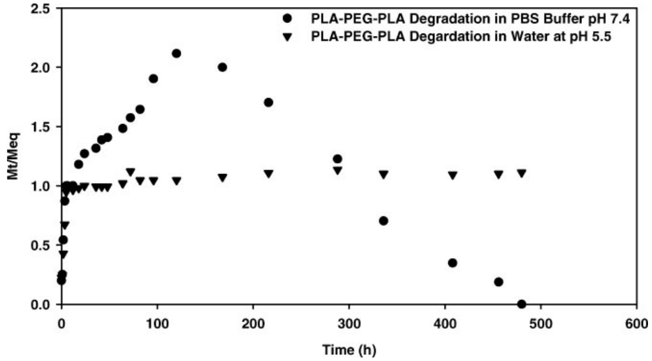

***Figure 1.***
A comparative study of PLA100 hydrogel degradation profile in PBS buffer (pH 7.4) and in water (pH 5.5) over 20 days at 37 °C.

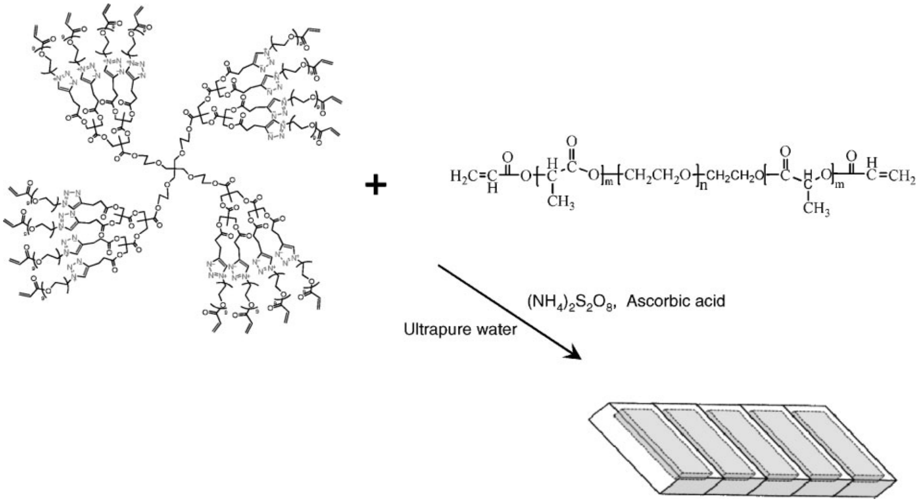

*Figure 2.*
Synthesis of Hydrogel from BH20 and acrylated PLA-b-PEG-b-PLA (PLA).

crosslinked PLA hydrogels displayed a much greater and faster swelling in water than the pure PLA hydrogels. The swelling ratios of the BH20 based hydrogels showed at least a two fold increase as compared to the PLA hydrogels (see Figure 3). This can be attributed to the formation of a highly porous morphology which could be the result of clustering of BH20 groups during the copolymerization process. This clustering can give rise to phase separation, and therefore yield high porosity and high swelling ratios. The high swelling ratio of hydrogels with high BH20 contents can also be related to faster intra-molecular crosslinking between the different arms of the acrylated-BH20, and consequently lower intermolecular crosslinking with PLA. Such behaviour can be clearly observed in dilute polymerizing solutions (see Figure 4 as

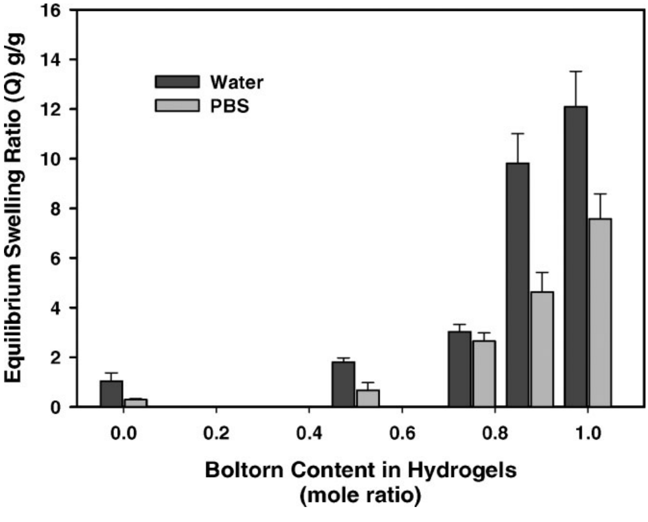

*Figure 3.*
Equilibrium swelling ratios of Boltorn (BH20) based Hydrogels in water and PBS buffer.

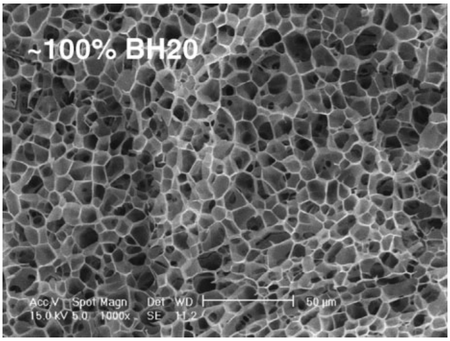

***Figure 4.***
Cryo SEM of Boltorn based hydrogel (94 mole% acrylated Boltorn: 6 mole% acrylated PLA-PEG-PLA triblock copolymer.

example of a cryoSEM image of a fully-hydrated BH20 gel).

## Conclusion

The swelling and degradation behaviour of PEG/ PLLA-PEG-PLLA hydrogels showed a close relationship between the hydrophilicity and PEG content. Degradation of the hydrogels was pH-dependent as a result of the hydrolysis of ester bonds in the lactide units of the triblock copolymer. In this work, it has been shown that hydrogel properties can be easily controlled by tailoring polymer composition for a specific purpose. In conclusion, the work will serve as a blueprint for further development of sophisticated hydrogels using Boltorn as a macromer component, where porous morphologies and high swelling ratios were observed.

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