Inter-penetrating Polymer Network Hydrogel Tissue Expanders with Controlled Expansion and Anisotropic Properties

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***Abstract*—Self-inflating hydrogel tissue expanders with controlled and anisotropic properties are highly pursued in today's plastic and reconstructive surgeries. This study designs an interpenetrating polymer network (IPN) self-inflating hydrogel tissue expander by crosslinking poly (DL-lactic-co-glycolic acid) (PLGA) in the presence of a poly (N-vinyl-2-pyrrolidone-co-methyl methacrylate) (VP/MMA) gel base. PLGA was functionalized with acrylate end-capping before the crosslinking. The swelling behavior and the mechanical properties of the IPN hydrogels with different PLGA contents were studied and compared to plain VP/MMA hydrogels. The initial and overall expansion rate was decreased with increasing PLGA content, while the equilibrium swelling ratio decreased with an increase in PLGA crosslinking density. The delayed expansion of IPN hydrogels is attributed to the increased hydrophobicity of the networks, which is verified by the increasing values of the Flory-Huggins interaction parameter ( ). Anisotropic IPN expanders were prepared by hot pressing IPN xerogels at 161℃. Their controlled and anisotropic properties give the IPN hydrogels a great potential in the plastic and reconstructive surgeries.**

***Index Terms*—IPN, VP/MMA, PLGA, tissue expander**

I. Introduction

Plastic and reconstructive surgery often requires additional soft tissue, especially skin. The inadequacy of sources and the lack of a good colour and texture match have prevented the more widespread use of using free grafts. The most common method is to place balloon expanders near the surgical site. However, there are many complications associated with their use, especially with repeated filling through a port. Thus, a new material with self-inflating properties is desirable.

Hydrogels have great potential because of their excellent biocompatibility and a variety of design options for different structures and swelling behaviors. Hydrogels are 3D lattices containing both hydrophilic and hydrophobic parts that can self-expand in aqueous media without dissolving. Generally speaking, hydrogels can expand up to several times their initial volume. Hydrogels are called smart materials because they can react to changes in the environment and respond with a functional reaction (e.g. swelling, shrinking, sol-gel conversion). And the swelling behaviour can be tuned by changing the polymerization conditions [1], [2] of the hydrogels.

In 1993 Wiese [3] introduced the copolymer of meth-methacrylate(MMA) and vinyl-pyrrolidone(VP) as an osmotically driven hydrogel tissue expander. As the dry gel absorbs body fluids, its volume increases and stretches the skin to generate more skin tissue without any external intervention. Since then they have been used in congenital anophthalmia [4], breast reconstruction [5] and cleft palate repair [6] albeit with limited success. The application has been limited largely because of the over-rapid expansion rate and the un-controlled swelling which leads to tissue necrosis [7] and other complications.

The most widely used method right now of controlling the over-rapid expansion is to wrap the hydrogel with a semi-permeable silicone membrane [8]. However, surgeons often wish to craft the prepared expanders into suitable shapes for fitting in irregular shaped defects. Thus the silicone membrane could be quite an inconvenience in real plastic surgeries.

Interpenetrating Polymer Network(IPN) refers to multicomponent materials consisting of two or more crosslinked networks in which at least one is crosslinked in the presence of another [9]. The polymer networks are topologically interlaced and entangled but not covalently bonded to each other, which gives IPN the advantage of retaining the properties of each network and the proportion of each network can be varied independently [10]. IPN is emerging as a promising way to change the properties of hydrogels without compromising the original characteristics of the polymer networks [11]-[13].

Poly(lactic-co-glycolic acid) (PLGA) is a popular FDA-approved polymer which is widely used as a biocompatible and biodegradable component in materials used for drug delivery, tissue engineering scaffolds, and screws in orthopaedics [14], [15].

In this paper, we aim to design an IPN hydrogel tissue expander by crosslinking functionalized PLGA in the presence of a VP/MMA hydrogel base. PLGA, as the secondary polymer network, is expected to restrict the gel base from swelling when immersed in tissue fluid. As PLGA is biodegradable [16] and its degradation products can be resorbed through the metabolic pathways, we expect it to diffuse out of the IPN system, leaving the gel

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with more ability to expand over time in a controlled manner. The degradation period of PLGA will depend on its monomer ratio [17] of lactic and glycolic acid. Thus manipulating PLGA monomer ratio can also influence the swelling period of the IPN tissue expanders. In this way, by changing the content ratio of the two polymer networks, the IPN system can create a controlled and delayed expansion.

Another great limitation of hydrogel tissue expanders is their isotropic properties, meaning swelling happens in a 3D mode, identically in every direction. In plastic and reconstructive surgeries, unwanted tissue growth in one direction will only bring attendant risks, unnecessary extrusions, and inconveniences. Anisotropic hydrogel tissue expanders are highly desirable in surgeries such as cleft palate defects, eyelid or nasal reconstruction, and the release of congenitally fused digits (syndactyly). Former work in the group [18] has successfully prepared anisotropic VP/MMA hydrogel expanders by annealing the xerogel under its glass transition temperature and then cooling under a compressive load. In this paper, we prepared anisotropic VP/MMA-PLGA IPN hydrogels in the same way and compared their properties with plain hot-pressed VP/MMA gels.

PLGA has hydroxyl groups at both ends and cannot be crosslinked directly. In this work, we managed to functionalize PLGA (monomer ratio 50:50) to end-cap it with –C=C– groups so that it can be crosslinked in the presence of the VP/MMA gel base. Fig. 1 shows the schematic of the modification of PLGA with hydroxyl groups at the ends to acrylate groups.

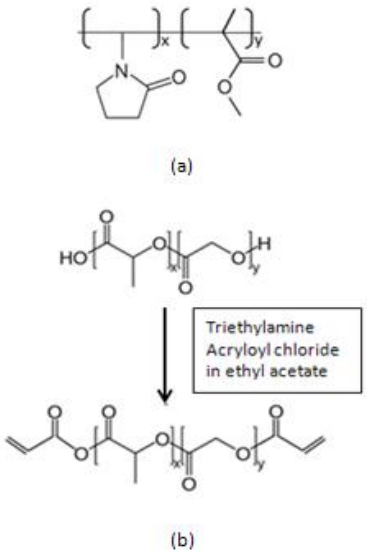


Figure 1. (a) Chemical structure of VP/MMA copolymeric gel and (b) Schematic of the modification process of PLGA with hydroxyl groups to acylate end groups.

II. Experiments

A. Chemicals

VP/MMA copolymeric dry gels with 9:1 monomer weight ratio of VP to MMA. VP/MMA gels were prepared by thermal polymerization with alkyl methacrylate (0.2wt%) as the crosslinker and azobisisobutyronitrile (AIBN) (0.2wt%) as the initiator by Polymeric Science Ltd (New Ash Green, UK). PLGA (50:50 lactic: glycolic acid) were purchased from Evonik Corporation, Birmingham Laboratories, US. The glass transition temperature, the weight average molecular weight (M_w) and polydispersity index (PDI) of PLGA were 30.5℃, 20kDa, and 2.0, respectively. Acryloyl chloride, triethylamine, anhydrous ethyl acetate, n-hexane, and dichloromethane (DCM), N, N'-Methylenebisacrylamide were purchased from Sigma-Aldrich (UK) and are used without further purification.

B. Preparation of IPN Hydrogels

Functionalized acrylate end-capped PLGA macromer was dissolved in organic solvent in three different concentrations, which is 0.025g/ml, 0.05g/ml, 0.1g/ml, respectively. IPN samples with different PLGA content (in organic solvent) were denoted as vmplga0.025, vmplga0.05, and vmplga0.1, respectively. The solutions were stirred for about 1 day. VP/MMA gels were then added in the solvent along with the crosslinking agent BIS, and the initiator AIBN. The solution was kept in the water bath at 37℃ for another 5 days to induce the formation of a crosslinked PLGA network penetrating through the hydrogel. After that the IPN hydrogels were washed with distilled water and dried under vacuum at 50℃ for 2 days to remove the residual solvent.

C. Swelling Behavior Tests

Swelling Measurements were carried out in distilled water at 37℃. The cylinder shape IPN hydrogels were taken out at specified time points and removed of excess surface water with filter paper. Their average diameters, heights and masses were measured and volume and mass expansion ratio were then calculated. The hydrogels were taken out for measuring and returned to the solution until they reached the maximum swelling state. The solution was replaced daily to remove any PLGA fragments that may have degraded or diffused out of the IPN hydrogels.

The degree of hydrogel expansion is usually measured as mass change ratio at intervals of time period. Volume change ratio is focused here instead of mass change because volume change is much more important for tissue expanders.

Volume swelling ratio Q_v is expressed in the same way as the mass swelling ratio, which is the volume change in the hydrogel at the time of measurement divided by the original volume of the xerogel, as in (1), where V_t stands for volume of the hydrogels at time t, and V_0 stands for the original volume of the xerogels before immersing them in the distilled water.

$$Q_v = \frac{V_t - V_0}{V_0} \times 100\% \quad (1)$$

Equilibrium swelling ratio $Q_{v\infty}$ refer to the volume swelling ratio at the time when the IPN hydrogels reached the equilibrium state as expressed in (2) below, where V_∞

stands for the volume of the hydrogels at the time when equilibrium swelling is reached.

$$Q_{v\infty} = \frac{V_\infty - V_0}{V_0} \times 100\% \quad (2)$$

D. Mechanical Properties

The samples were compressed under a dynamic mechanical analyzer (DMA) (Mettler Toledo SDTA861e) at their fully swollen state (equilibrium state). The compression tests were performed at room temperature and in a compression mode with an applied compressive strain ranging between 0.1% and 5% at 1Hz. The values of G were calculated from the slope of the linear part of the stress-strain curves.

E. Preparation of Anisotropic IPN Hydrogels

VP/MMA-PLGA IPN gels (dry state) were prepared in cylinders about 7mm in diameter and 10mm in height weighing approximately 0.4g. These dried gels and plain VP/MMA xerogels in similar shapes were put in a thermostatically controlled hydraulic press (Specac Ltd. UK) and heated to 161^{0}C. The gels were compressed to approximately 2mm thickness using brass moulds. The gels were left to cool to room temperature while retaining the compressive load.

F. Swelling Behaviours of Anisotropic IPN Hydrogels

IPN hydrogel cylinders were pressed into flat plates during the anisotropic processing. The gels were then placed in vials filled with pH=7.4 phosphate buffer saline (PBS) and incubated at 37℃. After predetermined time intervals, the samples were taken out to measure the diameters and heights after removing the excess surface water with filter paper. PBS solution was replaced daily to remove any degradation products from PLGA that may have diffused out of the gel into the solvents.

The diameter and height change ratio were measured and plotted as a function of time, separately.

While diameter change ratio stands for the swelling ratio in the direction perpendicular to the compression, height change ratio can tell us the swelling degree in the direction parallel to the compression. The diameter change ratio Q_d refers to the diameter change degree as expressed in (3), where D_t stands for the diameter at time t, and D_0 stands for the original diameter of the gels before immersed in the PBS solution.

$$Q_d = \frac{D_t - D_0}{D_0} \times 100\% \quad (3)$$

The height change ratio Q_h is expressed in the same way as in (4), where H_t stands for the height at time t, and H_0 stands for the original height of the gels before immersed in the PBS solution.

$$Q_h = \frac{H_t - H_0}{H_0} \times 100\% \quad (4)$$

III. Results and Discussions

A. Swelling Behaviour of VP/MMA-PLGA IPN Hydrogels

The swelling behaviour of the VP/MMA-PLGA IPN hydrogels with different PLGA content was investigated in distilled water at 37℃ and compared with plain VP/MMA hydrogels with similar shapes. Fig. 2 shows the swelling behaviour of the IPN hydrogels as a function of time with different PLGA contents. When prepared in DCM solutions, samples with PLGA concentration of 0g/ml, 0.025g/ml, 0.05g/ml, and 0.1g/ml are denoted as vm, vmplga0.025, vmplga0.05, vmplga0.1, respectively.

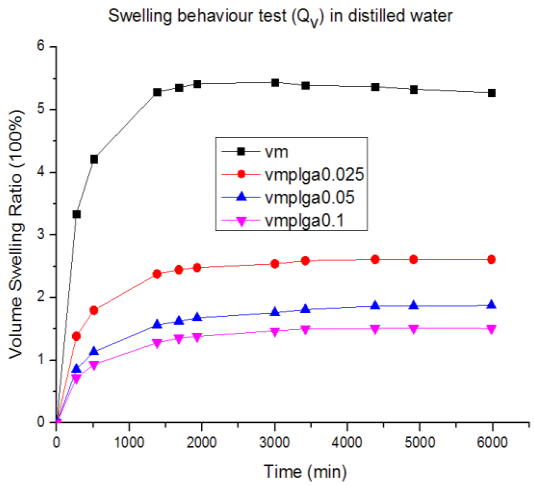


Figure 2. Volume Swelling Ratio of the IPN hydrogels and plain VP/MMA gels in distilled water.

The volume swelling ratio of all hydrogels initially increased rapidly and then slowed to an asymptotic value. The time required to reach the equilibrium state is defined as t_e here. At a specific time point, the slope of the curves is described as the swelling rate at every particular time point. The steeper the curve climbs in the beginning, the faster the hydrogels swell in the distilled water, the higher the swelling rate. It is clearly observed that the incorporation of PLGA into the hydrogel tissue expanders largely delayed the expansion rate at the beginning, which is a desired feature to leave enough time for the incision to heal in clinical trials. PLGA also decreased the expansion rate in the overall process, giving the skin cells enough time to generate new cells and avoid tissue necrosis. And the greater the PLGA content the more it decreased the swelling rate at the beginning and in the overall expansion process.

The introduction of PLGA into tissue expanders not only decreases the expansion rate, but also extends t_e, the time needed to reach an equilibrium swelling state. As can be seen in Fig. 2, it takes the plain VP/MMA hydrogel only about 1 day (1500min) to reach the maximum swelling state. For the IPN hydrogels, the t_e is more than 3 days, and the t_e of vmplga0.05 and vmplga0.1 can be as high as 4150min and 4980min, respectively. The maximum swelling ratio is decreased with the introduction of PLGA into the hydrogel expanders. This is considered to be the smaller network mesh size brought by the crosslinking of PLGA into the primary VP/MMA network. Moreover, PLGA is highly

hydrophobic, which will reduce the amount of water uptake. However, as PLGA is biodegradable, it will diffuse out of the hydrogel, leaving the network with more free space and less hydrophobicity. It is expected that with the degradation of PLGA, the swelling ratio will continue to increase over time and may catch up with that of the plain VP/MMA hydrogels.

B. Compressive Modulus E

Fig. 3(a) shows a typical stress-strain curve for the VP/MMA-PLGA IPN hydrogel, in the fully swollen state at room temperature. The slope of the linear part of the curve is the elastic modulus E which represents the gel strength. It might be expected that with the interpenetration of a crosslinked PLGA network into the hydrogel, the polymer density and the overall crosslinking density of the hydrogel network would both increase. And according to many previous research works, increased crosslinking density of the IPN hydrogel will lead to an increased modulus [19], [20]. However, Fig. 3(b) shows the modulus of the IPN hydrogels is decreasing when PLGA content is increasing in the system. The PLGA content here is the weight content in the dry IPN samples, with 0.44, 0.58, and 0.78 PLGA weight content correspond to samples vmplga0.025, vmplga0.05 and vmplga0.1, respectively. The modulus falls from about 200kPa to 150kPa when PLGA content was increased from 0% to about 80%.

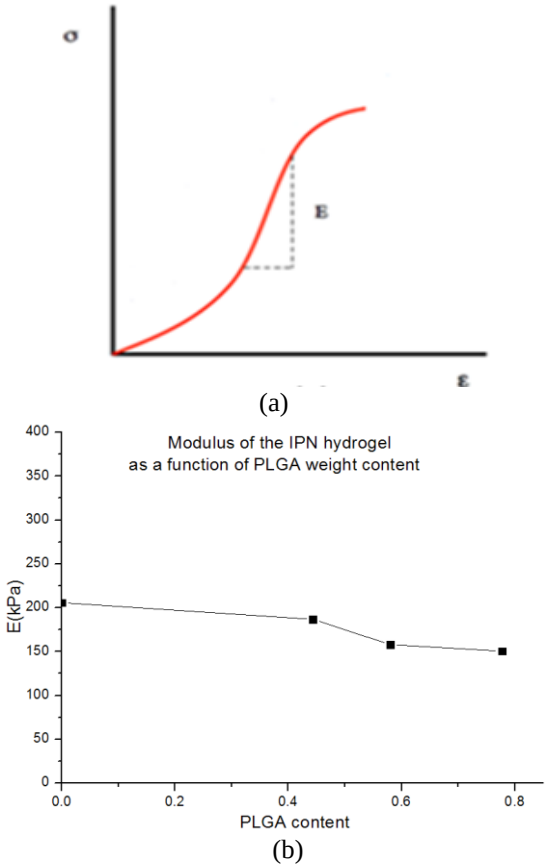


Figure 3. (a)A typical stress-strain curve for an IPN hydrogel. (b) Modulus change of the IPN as a function of PLGA weight content.

The decreasing modulus of the hydrogels could be the result of the relatively low glass transition temperature (T_g) of PLGA 50:50(T_g=31℃ as measured by DSC) compared to the T_g of the VP/MMA gel base (161℃ by DSC). Thus, the PLGA component may have brought in more mobility of the polymer chains and a higher free volume as well. Overall, it leads to a decreasing value of modulus. A decreased modulus induced by a lowered glass transition temperature has also been observed by other, e.g. [21]. Therefore, it can be concluded that the modulus of the VP/MMA-PLGA IPN hydrogels are influenced by the glass transition temperature of the secondary polymer component. The polymer network with a relatively lower glass transition temperature will act like a plasticizer in the IPN system and cause the modulus to decrease as more secondary polymer is incorporated in the gel base. It is also believed that the degree of the degradation of the secondary network will affect the value of modulus over time, which will be reported in a future article.

C. Flory-Huggins Interaction Parameter x

The Flory-Huggins theory with a Flory χ parameter fitted to network swelling data was used in order to obtain a reasonable value of the polymer-solvent interaction parameter. The Flory-Huggins model consists of the elastic, mixing and ion contributions. And for swelling in distilled water, as in (5), (6) and (7), the Flory-Huggins Interaction Parameter can be obtained using data collected in the swelling behavior tests and mechanical tests as stated above. In (5), (6), and (7), ϕ stands for the volume fraction of polymer in the gel, D_0 refers to the diameter of the xerogel, D is the diameter of the fully swollen gel, G means the elastic modulus derived by compression tests, γ_e is the crosslinking density, R is the universal gas constant, T is the absolute temperature at which the experiments were done, f stands for the functionality of the crosslinker, V_1 is the molar volume of the swelling liquid (for distilled water, V_1=18cm^3).

$$In(1-\Phi)+\Phi+\chi\Phi^2+\gamma_e V_1\left(\Phi^{1/3}-2\Phi f^{-1}\right)=0 \quad (5)$$

$$\Phi=\left(\frac{D_0}{D}\right)^3 \quad (6)$$

$$G=RT\gamma_e\Phi^{-1/3} \quad (7)$$

Fig. 4 shows the Flory-Huggins Interaction parameter between the water molecules and the polymer chains of the VP/MMA-PLGA IPN hydrogel expanders as a function of PLGA concentration. Here the PLGA content is weight content in the IPN xerogels. As can be seen from the picture, the Flory-Huggins interaction parameter χ is increasing along with increasing PLGA content and showing a trend to deviate from 0.5 as well. The ability of polymer networks to absorb water depends mainly on the specific interaction between water molecules and polymer chains. According to the Flory-Huggins model [22], χ takes higher values if the polymer network is more hydrophobic in the solution. This agrees with the hydrogels becoming more hydrophobic with more PLGA

crosslinked into the gel base. The increasing χ also explains why there is a reduction in both the expansion rate and the equilibrium swelling ratio with increasing PLGA content. Thus, we can conclude that the hydrophobicity of the secondary biodegradable polymer network and its concentration in the IPN hydrogel tissue expander are important in controlling the expansion rate and equilibrium swelling ratio.

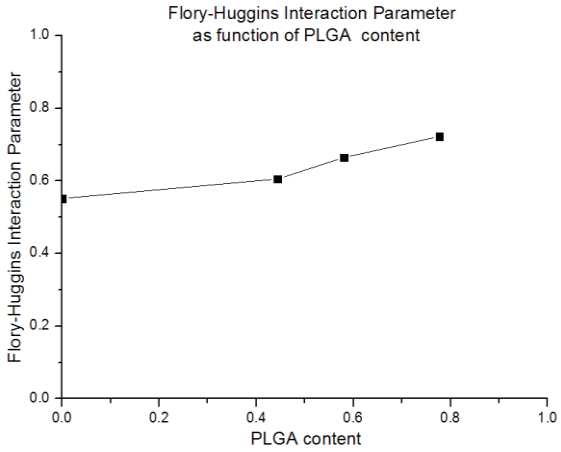


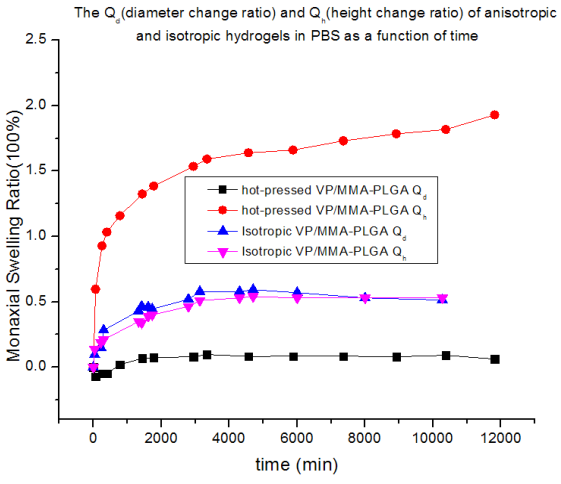
Figure 4. FFlory-Huggins Interaction Parameter as a function of PLGA weight content.

D. Anisotropic VP/MMA-PLGA IPN hydrogels and Their Swelling Behaviours in the Phosphate Buffer Solution(PBS)

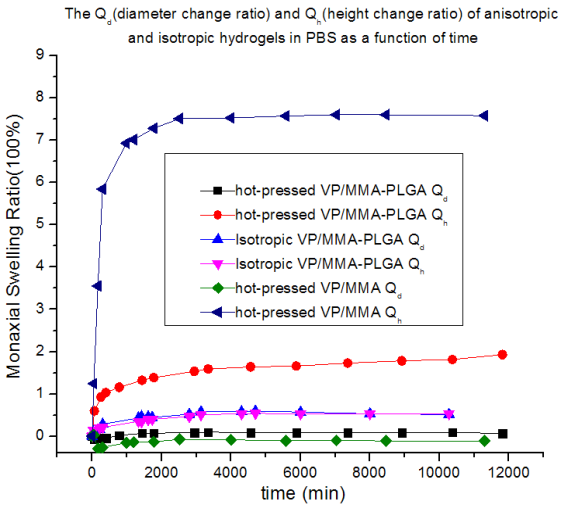
Fig. 5 shows shows the swelling behaviour of the anisotropic VP/MMA gels, isotropic and anisotropic VP/MMA-PLGA IPN gels in the phosphate buffer solution (pH=8.4) (PBS) as a function of time. The isotropic and anisotropic IPN gels have the same PLGA content and all the gels share the same size in the xerogel state. The diameter change ratio Q_d represents the expansion degree in the direction perpendicular to the compression. And the height change ratio stands for the expansion ratio in the direction parallel to the compression.

As can be seen from Fig. 5(a), the compressed VP/MMA-PLGA IPN gels displayed anisotropic properties, swelling up to 200% in height and the diameter remained almost unchanged. The untreated isotropic IPN gels can only expand about half of their original size but in all directions. This corresponds with previous work [18], that showed that hot pressing of the gels can produce anisotropic swelling gels, expanding predominantly in the direction parallel to the compression direction.

Fig. 5(b) has added the swelling behavior of isotropic plain VP/MMA gels to those of the IPN gels, pressed and untreated. Hot pressed plain VP/MMA gels also show anisotropic properties, with a fast swelling of 800% in height within 2500 mins and an almost unchanged diameter. The difference is it takes only about 2300 mins for the VP/MMA gels to reach the equilibrium swelling in height, but the expansion in height of the IPN gels kept increasing slowly during the 12000mins. As the slope of the curves at a specific time t can be seen as the expansion rate of the hydrogels in PBS, it is obvious that the IPN anisotropic gels have a much slower expansion rate and a much longer expansion period than the plain VP/MMA anisotropic gels. As has been explained earlier in this paper, the hydrophobicity of the PLGA network in the IPN anisotropic gels could be responsible for the decreased expansion rate and maximum expansion ratio. Since there is no change in the chemical structure between hot-pressed and untreated gels, as has been verified by FTIR, the hydrophobic biodegradable PLGA network is restricting the hydrogel from expansion uni-directionally and preventing the water molecules from getting in. PLGA secondary network is still playing an important part delaying the expansion process of the IPN gels.



(a)



(b)

Figure 5. (a) Comparison of diameter and height change of hot pressed IPN gels and untreated IPN gels. (b)Diameter and height change of hot pressed VP/MMA gels added to (a).

IV. CONCLUSION

VP/MMA copolymeric hydrogel based IPN hydrogels with varied PLGA contents have been successfully prepared with functionalized PLGA with –C=C– end

groups. The expansion rate as well as the equilibrium swelling ratio was found to decrease as the PLGA content increased. The increased Flory-Huggins interaction parameter of the IPN swollen gels indicates an increasing of hydrophobicity, which accounts for the swelling bevaviors.

The unexpected decreasing modulus of the swollen gels with increasing PLGA content has been attributed to the low T_g of PLGA, which gives more mobility to the polymer chains.

Overall, it is now possible to create an IPN self-inflating tissue expander with delayed and controlled expansion. The hydrophobicity and T_g of the biodegradable secondary polymer network have an important role controlling the expansion rate, equilibrium swelling ratio, and the mechanical properties. By tailoring the PLGA weight content in the IPN expander system we are now able to slow down the swelling process and predict the volume of the new tissue generated. The ability to be crafted and controlled should make this IPN tissue expander more attractive for a number of specific biomedical applications.

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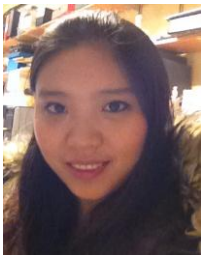

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