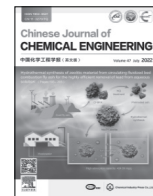




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Full Length Article

Foaming biocompatible and biodegradable PBAT/PLGA as fallopian tube stent using supercritical carbon dioxide

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ABSTRACT

Tubal pregnancy is a common abnormal pregnancy manifestation, and the ordinary conservative treatment of tubal adhesion usually leads to the rupture of fallopian tube, which increases the risk of a second ectopic pregnancy. To avoid this symptom, it is suitable to implant a stent to separate the adhesion. Here we prepared the PBAT/PLGA foam as the stent material using supercritical CO₂ foaming technology. With uniform macroporous structure and thin-wall feature, the foam possessed low compressive modulus in prevention of the possible second injury to the fallopian tube. The introduction of PLGA 50/50 improved the biodegradable capability of the foam, with a mass loss about 20% after a 12-week hydrolysis. After implanted into the ruptured fallopian tube of the rabbit model, the foam displayed excellent biocompatibility, and provided a good support to prevent tubal adhesion. As such, this work provides the foam material as a promising candidate for fallopian tube stent to remedy the tubal adhesion.

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1. Introduction

Ectopic pregnancy is an abnormal manifestation in which a fertilized egg implants and develops outside of the uterine [1,2]. In recent years, the morbidity of ectopic pregnancy, as a common obstetrics and gynecology disease, has reached about 2% [3]. Of various ectopic pregnancies, tubal pregnancy is prone to induce the burst or rupture of the fallopian [4,5], and even becomes life-threatening [6]. In order to preserve female fertility, the conservative treatment is usually preferred, where the products of conception are stripped and the fallopian tube is reserved to the greatest extent [7]. In this treatment, however, fallopian tube adhesion always occurs, greatly increasing the risk of a second ectopic pregnancy in the future [2,8]. To avoid this situation, a stent can be embedded into the damaged area to thoroughly separate and support the collapsed site, so that the ruptured surface can be repaired and reconstructed with the powerful self-healing ability of its epithelial tissue without any adhesion. When the self-repair of the epithelia has been achieved, it is better that the added stent is naturally degraded without another operation [9]. In this regard, the stent should meet several essential requirements: (1) biocompatible with tissues and organs without triggering rejection reac-

tions; (2) soft enough to avoid a second injury to the ruptured fallopian tube; (3) biodegradable or bioabsorbable within half a year [10–12]. To meet these requirements, biocompatible polymer foams with suitable mechanical properties and good biodegradability [12–15] could be a good choice.

Supercritical CO₂ foaming process prepares porous materials at specific temperature and pressure with the help of the unique diffusion characteristics of CO₂ to the exclusion of additional solvents and any chemical agents [16–19]. Although the morphology and mechanical properties are changed, the chemical composition and intrinsic bio-related properties can be well preserved [17]. This superiority makes the technology widely applied in biological fields, especially in tissue engineering [15,17,19–22]. For instances, Mooney *et al.* [23] prepared a polylactic acid scaffold for bone tissue engineering. After a four-week cell cultivation *in vitro*, the scaffold was proven to be a quantified site for cell proliferation, and the introduction of hydroxyapatite or β -tricalcium phosphate induced the differentiation of bone cells. Barry *et al.* [24] foamed poly (ethyl methacrylate)/tetrahydrofurfuryl methacrylate for the purpose of chondrocyte culture and cartilage repair. To simulate the epidermis – dermis structure of skin, Montjovent *et al.* [25] prepared a bilayer film as bionic artificial skin based on thermoplastic polyurethane foams. Hou *et al.* [26] prepared the interconnected microcellular tubular poly(ϵ -caprolactone) scaffold for vascular tissue engineering, and cytoskeleton assay verified the scaffold favor-

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able for cell attachment and proliferation. However, the foaming materials have not yet been applied in the reproductive system.

Polybutylene adipate terephthalate (PBAT) is biodegradable thermoplastic with a melting point of about 120 °C [27–29]. As a biopolymer without any toxic decomposition products, its good biocompatibility allows it to coexist in harmony with cells and tissues. On the other hand, PBAT is a copolymer comprising aliphatic and aromatic segments. The existence of aromatic segments contributes good mechanical strength, while the aliphatic segments provide excellent toughness and elongation at break. In supercritical CO₂ foaming process, due to its good CO₂ solubility and moderate crystallinity degree, PBAT demonstrates good foamability, and tends to form macroporous structure with low modulus. However, the low melt strength originated from its linear chain structure is likely to lead to the collapse of macroporous morphology. To enhance the melt strength, commonly used modification approaches include blending, cross-linking, and chain extension [30]. Another drawback of PBAT is its comparably slow biodegradation rate, which is retarded by the aromatic segments [31,32].

Poly (lactic-co-glycolic acid) (PLGA) is another biocompatible semi-crystalline thermoplastic copolymerized by glycolic acid and lactic acid [33–37]. It has attracted widespread attention because of its particularly excellent biodegradability under hydrolysis conditions [12,31,36,37]. Due to a large number of ester groups in the main chain and the relatively simple repeating units, the biodegradation rate of PLGA is relatively fast. Without any enzymes, the biodegradation products of PLGA are glycolic acid, lactic acid and their oligomers, which are natural metabolites of human body, and can be converted into CO₂ and water, and finally excrete from the body completely. Currently, PLGA has been approved in clinical fields. The most well-known application of PLGA is as surgical sutures [38], which can be completely biodegraded in 60–150 days *in vivo*. The properties of PLGA, such as melting point, crystallinity degree, CO₂ solubility, and biodegradation rate, vary with its chemical composition and molecular weight. Generally, the increase of the glycolic acid content promotes the crystallinity, suppresses CO₂ solubility, improves the hydrophilicity, and accelerates the biodegradation [34,37]. The weakness of PLGA lies in its excessive rigidity and poor flexibility, thus a softening process is preferred [39].

Herein we prepared a biocompatible, biodegradable, and flexible foam as the fallopian tube sent material. Considering its good toughness, flexibility, CO₂ solubility, and biocompatibility, we selected PBAT as the foaming matrix, and introduced PLGA 50/50 to enhance melt strength of the foam, and to further improve its biodegradability. The mechanic strength and biodegradability of the selected foam material were then determined to evaluate its applicability, finally, the foam was embedded into the fallopian tubes of rabbits to avoid the adhesion of mucosal surface, and a model was established to evaluate the comprehensive performance of PBAT/PLGA foam *in vivo*. With the powerful regeneration of epithelia, the damaged site was repaired, while the stent can gradually decompose into small fragments and slowly fall off without a withdrawing operation, so as not to affect the thereafter reproductivity of the model.

2. Materials and Methods

In this work, PBAT and PLGA were firstly blended via melt blending process. Then the PBAT/PLGA foams with uniform and stable cellular morphology were prepared using supercritical CO₂. To verify whether the obtained foams could act as fallopian stent material, a foaming material with suitable structure and properties was implanted in the rabbit model with an endothelial injury at fallopian tubes. An experimental flow chart illustrates the

whole procedures, as demonstrated in Fig. 1. Detailed experimental operations are shown below.

2.1. Materials

PBAT (ecoflex C1200) was purchased from BASF SE, German. PLGA 50/50 was obtained from Tongliao GEM Chemical, China. The weight-average molecular weights of PBAT and PLGA were characterized with a gel permeation chromatography instrument (PL-GPC50, Agilent Technologies, USA) with values of about 90,000 and 7000 g·mol⁻¹. Liquid CO₂ with a purity of 99.9% was purchased from Beijing Yanglike Co., China.

2.2. Preparation of PBAT/PLGA blend

To avoid hydrolysis in the melt blending process, PBAT and PLGA should be dried in a vacuum oven for at least 4 hours in advance, so that moisture was completely removed. To achieve equivalence between biodegradability and foamability, PBAT and PLGA with a weight ratio of 75/25 were weighed, premixed, and blended in an internal mixer (XSS-300, Shanghai Kechuang, China) with a blending temperature of 185 °C, a screw speed of 60 r·min⁻¹ for 5 min. After water-cooling, pelleting, and drying, fine granules of PBAT/PLGA, as well as pristine PBAT, were molded into a thin film with a thickness of 2 mm with a plate vulcanizer (XH-406, Dongguan Xihua Testing Machine Co., Ltd., China) at 185 °C. After cooling down, the thin film was cut into square samples with a size of 12 mm × 12 mm, and stored in dry conditions to avoid moisture absorption.

2.3. Supercritical CO₂ batch foaming process

The cut square samples were placed into a stainless autoclave. Liquid CO₂ was pressurized and injected into the autoclave continuously with a plunger pump, until specific foaming temperature and pressure were reached in the autoclave. Then the plunger pump was stopped, the autoclave was sealed, and the samples were soaked in supercritical CO₂ for 3 h. After the pressure in the autoclave was depressurized rapidly to atmospheric pressure, the PBAT and PBAT/PLGA foams were obtained. Specifically, the foaming temperatures of 108 °C, 114 °C, and 120 °C and the pressures of 12 MPa, 16 MPa, and 20 MPa were considered to find a suitable foaming condition.

2.4. Differential scanning calorimetry (DSC)

Thermal effects of the samples were analyzed with a DSC calorimeter (Q20, TA instrument, USA). 6–8 mg of each sample was tested in a N₂ atmosphere. The temperature was raised from room temperature to 250 °C. After holding for 10 minutes to eliminate the thermal history, the temperature was decreased to -80 °C, and then raised to 250 °C. Both the heating and the cooling rates were 10 °C·min⁻¹. The crystallinity in the PBAT phase, χ_c , was calculated with

$$\chi_c = \frac{\Delta H_m}{\omega \times \Delta H_0} \times 100\% \quad (1)$$

where ω is the mass fraction of PBAT, ΔH_m is the melting enthalpy of the test sample after eliminating the thermal history, and ΔH_0 is the standard melting enthalpy of PBAT with a value of 114 J·g⁻¹.

2.5. Cellular morphology observation and parameter calculations

To characterize the cellular morphology of PBAT and PBAT/PLGA foams, the cross-section morphologies of the foams were observed with a scanning electron microscope (SEM, Hitachi-S4700, Hitachi,

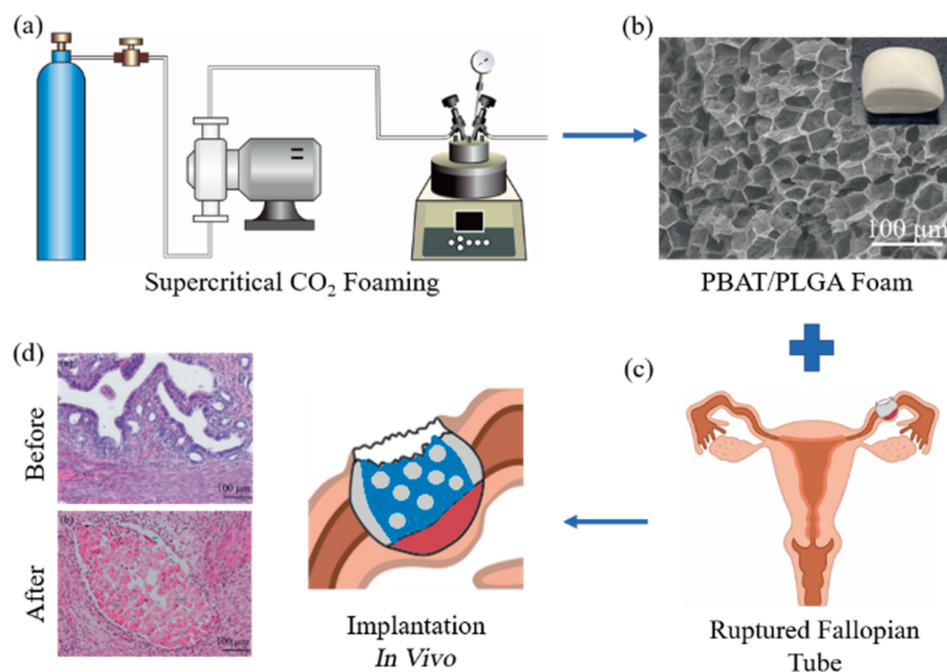


Fig. 1. Schematic visualization of the preparation and repair process of the PBAT/PLGA foam in a fallopian tube: (a) the device of the supercritical CO₂ foaming; (b) microscopic and macroscopic morphologies of the PBAT/PLGA foam; (c) female reproductive system with one side of ruptured fallopian tube; (d) *in vivo* implantation of the foam into the ruptured fallopian tube.

Ltd., Japan). The foams were soaked in liquid N₂ to avoid damaging the porous structure. The pore size, d , was directly evaluated through statistical average of all cells in a SEM micrograph. The volume expansion ratio (VER), ϕ , was calculated with

$$\phi = \frac{\rho_0}{\rho_f} \quad (2)$$

where ρ_0 and ρ_f are the densities of unfoamed and foamed PBAT/PLGA blends in g·cm⁻³. The density was measured with an electronic balance with a water displacement module. The cell density, N , was calculated by

$$N = \left(\frac{n}{A}\right)^{\frac{3}{2}} \quad (3)$$

where n and A are the number of cells and area in cm² of a SEM micrograph, respectively. Finally, the cell wall thickness, δ , was calculated with

$$\delta = \left(\frac{1}{\sqrt{1 - 1/\phi}} - 1\right)d \quad (4)$$

2.6. Compression tests

Compression tests were carried out with a universal testing machine (E43. 104, MTS Systems Corp., China). PBAT/PLGA foams were cut into cubic samples with a size of 12 mm, and were soaked in a phosphate buffered saline solution (PBS) at 37 °C and pH 7.4 for 1 h. The compressing velocity was set at 1.5 mm·min⁻¹. At least three parallel tests were required to ensure reliability of the tests.

2.7. Biodegradation experiments *in vitro*

A PBAT/PLGA foam with a foaming temperature of 120 °C and pressure of 16 MPa was selected for the following tests. The foam was cut into a thin film with a thickness of 2–3 mm. The film was soaked in a PBS solution at 37 °C and pH 7.4. Then the PBS solution

was placed in a temperature-controlled shaker with a temperature of 37 °C and a vibrating velocity of 15 r·min⁻¹. Three parallel experiments were required to ensure the reliability of the experiments. The degradation experiments lasted for 12 weeks in the unchanged PBS solutions. The films were taken out and weighed every week. Before weighed, the films were dried in an oven until their masses kept constants. The relative mass of each sample was calculated with

$$\text{relative, mass} = \frac{w_t}{w_0} \times 100\% \quad (5)$$

where w_0 and w_t are the masses before and after biodegradations.

In addition, to characterize the change of the cellular morphology over time, the cross-section morphologies of the biodegraded foam were observed every four weeks.

2.8. *In vivo* implantation at fallopian tubes

To validate the performance of the PBAT/PLGA foam *in vivo*, a rabbit model with an endothelial injury at fallopian tubes was established. All the protocols for animal experiments were performed according to the guidelines issued by the Ethical Committee of the Chinese Academy of Sciences (CAS), and were approved by the Ethical Committee of CAS. Initially, the rabbit was anesthetized, and the hair on the belly was shaved off in advance. Under the restrict aseptic condition, the abdomen was opened, and the fallopian tubes at both sides were cut open along the full length. The mucosal surfaces of the fallopian tubes were destroyed via electrocoagulation of an electrosurgical knife with a voltage of 45 W and a duration of 3 s. After two weeks, some tissues on the mucosal surfaces were picked up, stained with H&E and observed with an electron microscope to verify whether chronic inflammation existed at fallopian tubes.

In prior to the implantation, the prepared PBAT/PLGA foam should be sterilized and cut, with its shape in accordance with the size of the fallopian tube. After the cut piece was implanted into the fallopian tube at one side, the opened fallopian tube was

occluded with 3.0 absorbable sutures. As the blank group, the fallopian tube at the other side was directly occluded without implantation. Then the pelvic cavity was washed with 0.9% sodium chloride before the abdomen was closed. Thereafter, the intramuscular injection of ceftriaxone sodium (1 g dissolved in 3.5 ml 1% lidocaine hydrochloride) with a dosage of 50 mg·kg⁻¹ should be conducted for 3 d for prevention of infections. The rabbit was kept feeding to observe its daily state. After 3 weeks, the rabbit was euthanized. The fallopian tube with the implant was taken out and stained with H&E and observed with an electron microscope. Three parallel tests were performed to ensure reliability of the tests.

3. Results and Discussion

3.1. Cellular morphologies and parameters

Fig. 2 shows the DSC curves of the PBAT, PLGA and PBAT/PLGA samples. From the first heating scan of PLGA in Fig. 2(a), a cold crystallization peak appears at about 80 °C before the melting point. Due to the slow crystallization kinetics of PLGA, the crystal nuclei had not yet grown up before the chain segments froze. When the temperature rose, the chain segments began to move, these crystal nuclei continued to grow up and formed crystals. As a consequence, an exothermic crystallization peak appears in Fig. 2(a). With the introduction of the PLGA into the PBAT, a new melting peak appears at about 180 °C, corresponding to the melting process of the PLGA phase. In the second heating scan in Fig. 2(c), the two steps on the PBAT/PLGA curve at around -35 °C and 40 °C indicate the poor compatibility of PBAT and PLGA with a weight ratio of 75/25. Fig. 2(b) shows the DSC cooling scan after eliminating the thermal history. Because of the slow crystallization kinetics, no crystallization peak appears on the PLGA curve at the cooling rate of 10 °C·min⁻¹.

The crystallinities of the PBAT and PBAT/PLGA are summarized in Table 1. The introduction of PLGA suppressed the crystallization of PBAT because of the increased disorder in the blend.

In order to study the influence of the introduction of PLGA on the foaming of PBAT, the cellular morphologies of PBAT and PBAT/PLGA foams under the same foaming condition are shown in Fig. 3. In comparison of the PBAT/PLGA foam, the PBAT foam exhibits a larger average pore size with some broken cells due to its low melt strength of pristine PBAT. Generally, a larger pore size corresponds to a thinner cell wall. That is to say, the cell walls are too thin to support the loose structure. In this case, the interconnectivity between inner pores and outer atmosphere increased, thus the CO₂ molecules cannot be completely restricted in the pore cavities, and a large amount of escaped CO₂ resulted in the shrinkage of the foam at a macroscopic scale. On the contrary, the aver-

Table 1
Thermal properties of PBAT and PBAT/PLGA

	$T_c/^\circ\text{C}$	$\Delta H_m/\text{J}\cdot\text{g}^{-1}$	$\chi_c/\%$
PBAT	65.68	28.19	24.73
PBAT/PLGA 75/25	67.28	19.29	22.56

age pore size in the PBAT/PLGA foam is relatively small, which is attributed to the existence of the PLGA domains with high melting point, as is shown in Fig. 2(a). PLGA domains acted as the heterogeneous bubble nucleation sites, thereby improving the cell density. As a consequence, the PBAT/PLGA foam maintained its stable porous structure.

In order to optimize the foaming condition of the PBAT/PLGA foams as fallopian tube implant, several foams were prepared at different temperatures and pressures, and their cellular morphologies were characterized. The cellular morphologies of PBAT/PLGA foams at different temperatures in Fig. 4 reveal that the pore size increases with temperature. As the foaming temperature elevated, the solubility of CO₂ in the foaming matrix reduced gradually. Low CO₂ solubility brought about the reduced CO₂ supersaturation in the rapid depressurization process, leading to the increased nucleation free-energy barrier and decreased bubble nuclei [41]. Besides, the viscosity of the polymer matrix decreased with increasing temperature, which was beneficial to the diffusion of CO₂, thereby conducted rapid bubble growth. The co-effect of restrained bubble nucleation and motivated bubble growth caused larger pore sizes. Generally, pore size is positively correlated with VER but negatively correlated with cell density and cell wall thickness [40,42], which is consistent with the calculated cellular parameters, as listed in Table 2. By comparing the morphologies foamed at three different temperatures, we selected 120 °C as the foaming temperature.

Fig. 5 displays the SEM micrographs of the cellular morphologies of PBAT/PLGA foams at different foaming pressures. As the pressure elevated, the pore size gradually increased. Increasing pressure greatly improved CO₂ solubility in the foaming matrix. Therefore, more bubble nucleation sites appeared during the rapid depressurization, and finally a dense cellular morphology with small pores was formed [40]. Table 3 summarizes the corresponding cellular parameters. At the foaming pressure of 12 MPa, although the average pore size is much larger, the VER and cell wall thickness abnormally declines and increases, respectively. This is attributed to the shrinkage of the foams, which leads to the inaccuracy of the calculated cellular parameters. Such shrinkage foam should be avoided in the selection for thereafter implants. As the pressure was raised to 16 MPa, the foam displays stable macroporous structure with thinner cell walls, which is favorable to the improvement of the softness and biodegradation. When the pres-

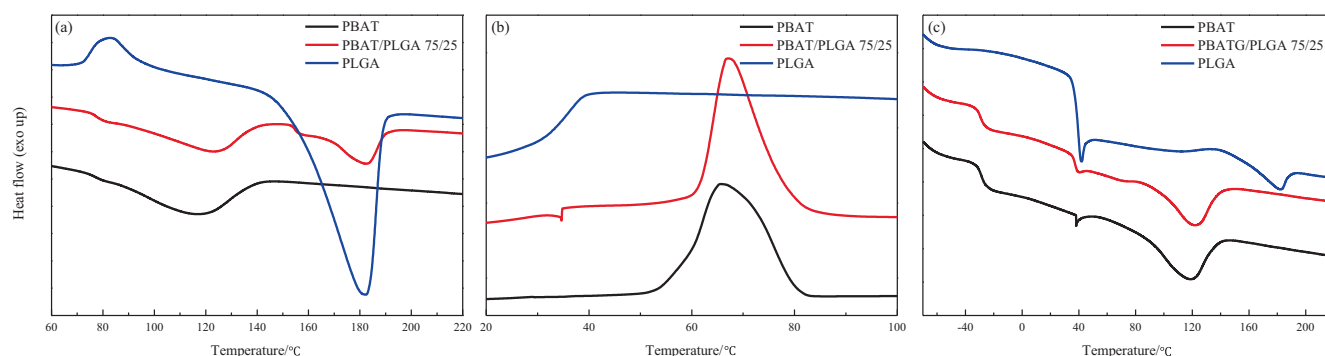


Fig. 2. DSC curves of the PBAT, PLGA and PBAT/PLGA samples: (a) the first heating scan, (b) the cooling scan, and (c) the second heating scan.

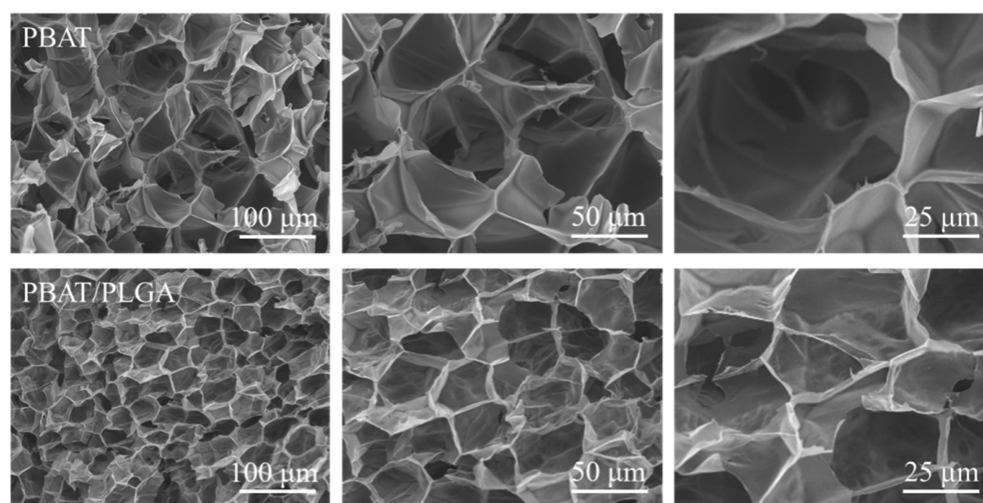


Fig. 3. Cellular micrographs of the PBAT and PBAT/PLGA foams formed at 120 °C and 16 MPa under SEM.

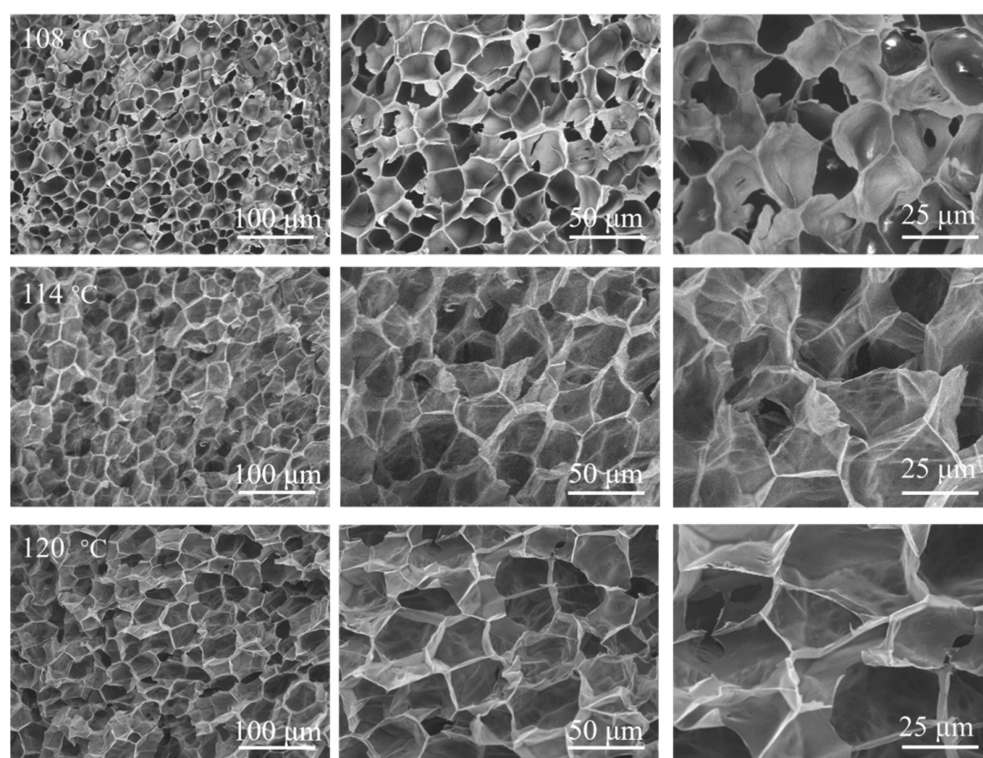


Fig. 4. Cellular micrographs of the PBAT/PLGA foams formed at different temperatures and 16 MPa under SEM.

Table 2

Cellular parameters of the PBAT/PLGA foams at the foaming pressure of 16 MPa

	108 °C	114 °C	120 °C
Cell size/ μm	20.38 ± 2.92	29.46 ± 3.95	35.96 ± 7.61
VER	8.19	12.28	24.36
Cell density $\times 10^{-7}/\text{cm}^{-3}$	10.83	4.07	2.16
Cell wall thickness/ μm	1.37	1.28	0.76

sure was further enhanced up to 20 MPa, the average pore size further narrowed down, resulting in thick walls. By combining Figs. 3 and 4, we think that the foaming condition of 120 °C and 16 MPa possesses the optimum structure.

3.2. Compressive tests

In previous studies and clinical trials, many surgeons believed that the conventional stents would destroy the cilia on the inner surface of fallopian tube and tried to avoid the implantation operation [43,44]. Therefore, low compressive modulus is essential for materials as tubal stents. Taking the actual scenario of the implants into account, the compressive characterization should be carried out in wet condition [45]. Fig. 6 shows the compressive stress-strain curves of the PBAT/PLGA foams under different foaming conditions. Each curve can be divided into three stages, which basically coincides with the conventional model of compressive behaviors of porous materials proposed by Gibson and Ashby [46]. In the initial stage of compression, the compressive stress is

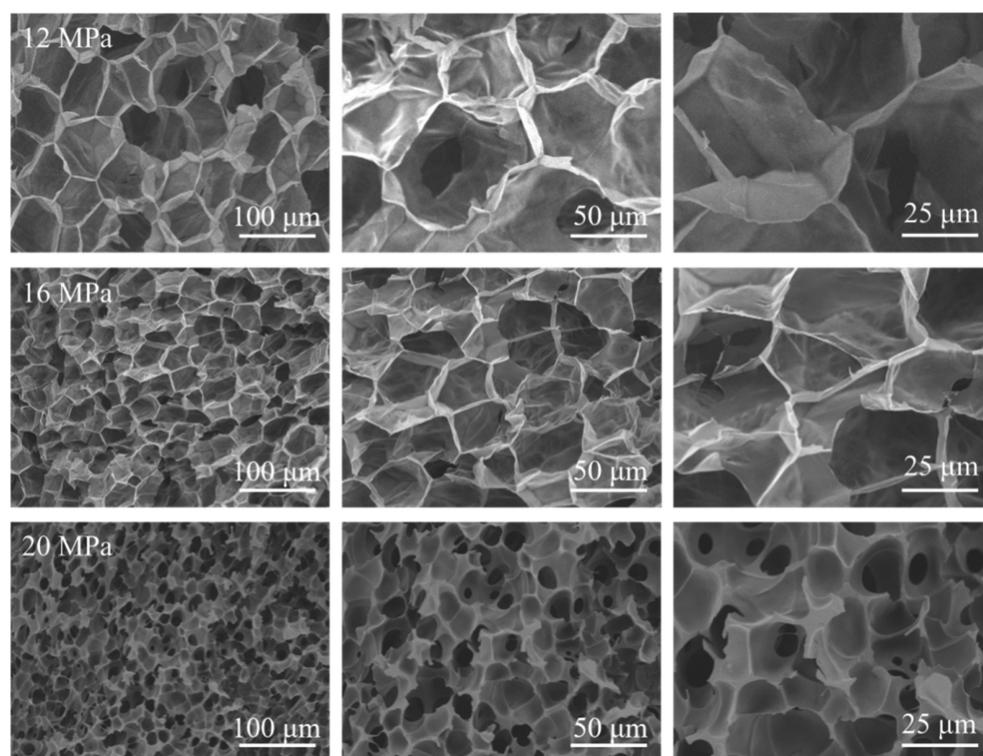


Fig. 5. Cellular micrographs of the PBAT/PLGA foams at different pressures and 120 °C under SEM.

Table 3

Cellular parameters of the PBAT/PLGA foams at the foaming temperature of 120 °C.

	12 MPa	16 MPa	20 MPa
Cell size/ μm	69.65 ± 11.07	35.96 ± 7.61	15.84 ± 2.29
VER	12.27	24.36	7.23
Cell density $\times 10^{-7}/\text{cm}^{-3}$	0.45	2.16	12.65
Cell wall thickness/ μm	3.02	0.76	1.22

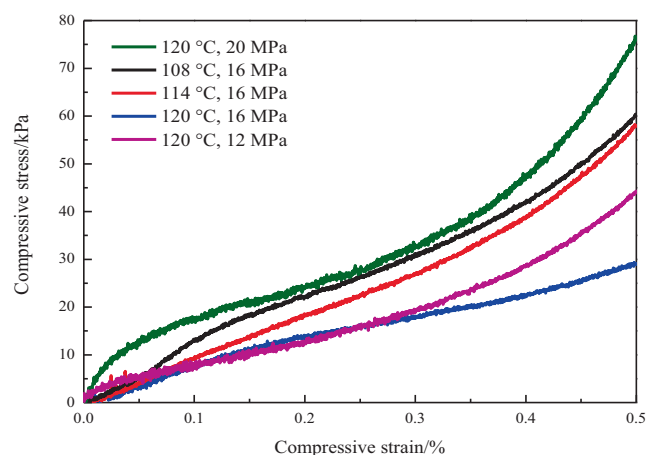


Fig. 6. Compressive stress-strain curves of PBAT/PLGA foams under different foaming conditions.

linearly correlated to the compressive strain, and the slope is defined as the compressive modulus. As the strain continued to increase, the growth rate of the stress slowed down, and the foam revealed a yielding behavior. With the continuous compression of the foam, the cells gradually ruptured, and the porous material became a dense solid, leading to a drastic rise of stress. By compar-

ing different curves, one can find that the compressive modulus and the yield stress increase with decreasing temperature and increasing pressure. The exceptional performance at 120 °C and 12 MPa is due to the cellular collapse. As an important index in tissue engineering, compressive moduli of the PBAT/PLGA foams under different foaming conditions are listed in Table 4. To avoid a second injury to the damaged fallopian tube brought about by the introduced stent, a low compressive modulus is preferred here. All PBAT/PLGA foams exhibited comparably low compressive moduli, with a minimum of lower than 0.1 MPa under the foaming condition of 120 °C and 16 MPa, which means that the PBAT/PLGA foams meet the mechanical requirement of fallopian tube stent.

3.3. Biodegradability of PBAT/PLGA foam *in vitro*

In order to repair the ruptured fallopian tube, the implanted stent should possess suitable biodegradable performance, so as not to affect the fertility of the patient. Such effect can be evaluated in the simulated hydrolysis experiment. As a part of internal environment, the fluid in fallopian tube has the similar composition with the body fluid [47,48]. PBS solution is a kind of buffer solution which has the similar osmotic pressure, ion concentration, and pH with the body fluid. Besides, because of the buffering effect, the PBS solution is suitable for experiments that simulating the body internal environment for a long duration, for example, the biodegradability experiment *in vitro*.

At given temperature and pH, the morphologic and mass variations of the foam after degradation were recorded macroscopically (relative mass) and microscopically (cellular morphology), and the corresponding results are given in Figs. 7 and 8. In the first few weeks, little difference can be perceived both macroscopically and microscopically. Eight weeks later, slight changes were observed in mass loss and cellular morphology. The mass of the foam decreased about 5%, and some small breakages appeared on the cell walls. After twelve weeks, an accelerated degradation rate

Table 4
Compressive moduli of the PBAT/PLGA foams under different foaming conditions

Foaming condition	108 °C 16 MPa	114 °C 16 MPa	120 °C 16 MPa	120 °C 12 MPa	120 °C 20 MPa
Compressive modulus/kPa	121.06 ± 10.57	88.53 ± 7.02	70.65 ± 13.38	218.73 ± 25.04	478.27 ± 19.75

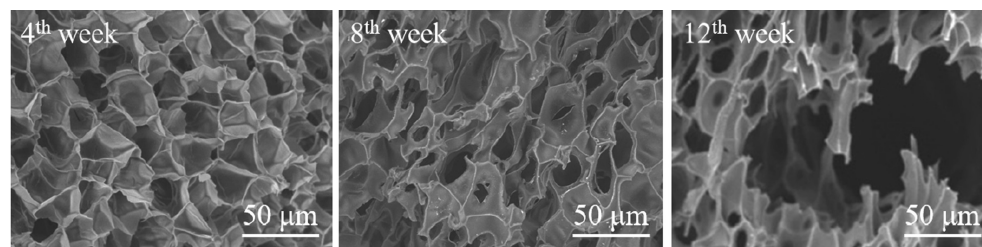


Fig. 7. Cellular morphologies of the PBAT/PLGA foam with different degradation times.

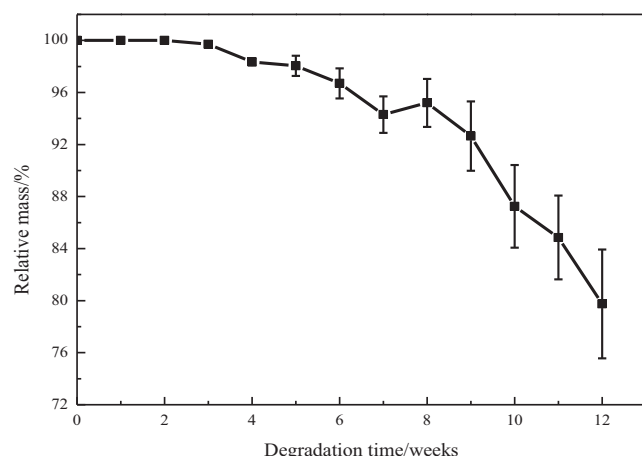


Fig. 8. Relative mass of the PBAT/PLGA foam as a function of degradation time.

was recorded. The mass loss enlarged to about 20%. In the SEM micrograph, the number of small breakages increase, and more importantly, some huge holes emerge, which is due to the collapse of several cells in this region. The whole degradation process can be divided into two stages. Initially, the material decomposed into oligomers with lower molecular weight. In this stage, no obvious changes can be found from the microscopic morphology, and the degradation products cannot be separated, thus the mass loss was insignificant. As the time passed by, the lower molecular weight of the oligomers was degraded into smaller segments and leached out from the bulk material. Therefore, the mass of the

material decreased, and erosions can be found in its microstructure [49].

In the degradation experiment, although the PBAT/PLGA foam not eventually disintegrated into fragments or completely disappeared due to the time limit, the degradation effect can be qualitatively evaluated. In fact, once the huge holes appeared in the foaming material, the framework was no longer stable, and the structure tended to collapse. Moreover, the triggering effect given by the surrounding cells, such as macrophages [50], could accelerated the actual hydrolytic degradation rate of the implanted foam in fallopian tube. In this situation, the remaining fragments would not affect the reproductivity of the patient. It seems that the degradation rate of PBAT/PLGA foam is suitable to act as the stent material.

3.4. Histological analysis of PBAT/PLGA foam in fallopian tube

In order to verify whether the ruptured fallopian tubes in rabbit model were successfully established, the tissues of the mucosal surfaces on the fallopian tubes before implantation were observed, as shown in Fig. 9(a). It can be clearly found that chronic inflammatory cell infiltration appeared, lymphocytes increased, epithelia shed, and cilia decreased or even disappeared. These results demonstrate that the fallopian tubes showed chronic inflammatory, and the animal model with epithelial damage in the fallopian tubes was successfully established. This pre-experiment provided the prerequisite for the following *in vivo* characterization of the PBAT/PLGA foam in the ruptured fallopian tubes.

After the PBAT/PLGA foam was implanted, the rabbits had no significant abnormality in their daily state. In the histological analysis of tissues in the fallopian tubes with implantation, as shown in

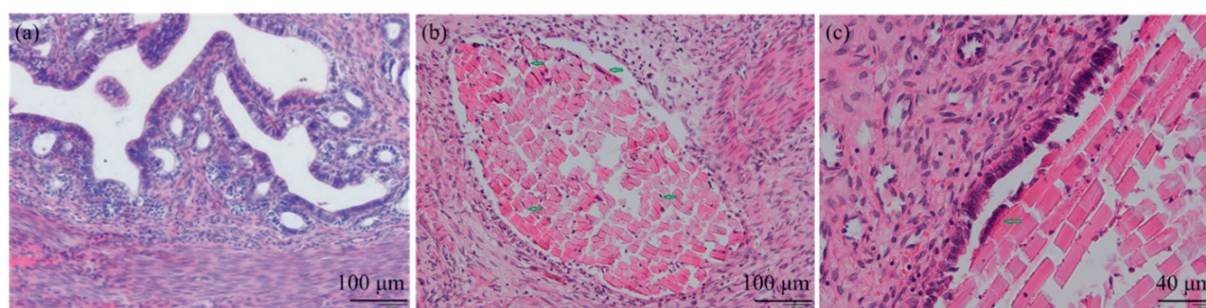


Fig. 9. Histological morphologies of tissues in the collapsed fallopian tubes (a) before implantation, (b) after implantation at low magnification and (c) at high magnification.

Fig. 9(b) and 9(c), the PBAT/PLGA foam was surrounded by the mucosal epithelia in the lumen, meanwhile its porous structure maintained. Some cells adhered or crawled along the surface of the implant, as instructed by the arrows, suggesting a good biocompatibility of the implant. Compared with the histological morphology before implantation, the inflammatory cell infiltration was alleviated by the stent without any tubal adhesion. This result was attributed to the decoupling function of the stent and the self-repair of the surface epithelia. Further studies will focus on the antibacterial performance, and reproductive toxicity of the implants in the near future.

4. Conclusions

With supercritical CO₂ foaming process, the PBAT/PLGA foams were prepared. The introduction of PLGA enhanced the melt strength of the foaming systems, thus the PBAT/PLGA foams exhibited uniform and stable macroporous structure. In compression tests, the foams displayed low compressive moduli, which are helpful to prevent possible harm to the tissues at fallopian tube. By considering the optimum structure and properties, the foam formulated at 120 °C and 16 MPa was selected for further evaluation. The hydrolysis experiment *in vitro* verified that the introduction of PLGA 50/50 ensured a rapid biodegradation of the foam in simulated internal environment, with a mass loss of about 20% after a 12-week degradation. After the foam was implanted *in vivo*, it displayed excellent compatibility with the surrounding tissues in the ruptured fallopian tube, and verified the capability to support the damaged site, which met the requirements for recovering adhered fallopian tubes. These results have proven that the PBAT/PLGA foam has the potential application as fallopian tube stent.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

- [1] P.S. de Silva, H.H. Hansen, S. Wehberg, S. Friedman, B.M. Nørgård, Risk of ectopic pregnancy in women with inflammatory bowel disease: A 22-year nationwide cohort study, *Clin. Gastroenterol. H.* 16 (2018) 83–89.
- [2] Committee on Practice Bulletins–Gynecology, ACOG practice bulletin No. 191: Tubal ectopic pregnancy, *Obstet. Gynecol.* 131 (2018) 65–77.
- [3] J.Y. Hsu, L. Chen, A.R. Gumer, A.I. Tergas, J.Y. Hou, W.M. Burke, C.V. Ananth, D.L. Hersham, J.D. Wright, Disparities in the management of ectopic pregnancy, *Am. J. Obstet. Gynecol.* 217 (2017) 49.
- [4] J.L.V. Shaw, S.K. Dey, H.O.D. Critchley, A.W. Horne, Current knowledge of the aetiology of human tubal ectopic pregnancy, *Hum. Reprod. Update* 16 (2010) 432–444.
- [5] D. Saxon, T. Falcone, E.J. Mascha, T. Marino, M. Yao, T. Tulandi, A study of ruptured tubal ectopic pregnancy, *Obstet. Gynecol.* 90 (1997) 46–49.
- [6] R. Ngui, S. Ravindran, D.B.L. Ong, T.K. Chow, K.P. Low, Z.S. Nureena, Y. Rajoo, Y. T. Chin, A. Amir, A.F. Ahmad, Y.A.L. Lim, R. Mahmud, Enterobius vermicularis salpingitis seen in the setting of ectopic pregnancy in a Malaysian patient, *J. Clin. Microbiol.* 52 (2014) 3468–3470.
- [7] P.J. Hajenius, F. Mol, B.W.J. Mol, P.M.M. Bossuyt, W.M. Ankum, F. van der Veen, Interventions for tubal ectopic pregnancy, *Cochrane Db. Syst. Rev.* 1 (2007) 1–104.
- [8] The American Fertility Society, The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Müllerian anomalies and intrauterine adhesions, *Fertil. Steril.* 49 (1988) 944–955.
- [9] J.F. Gauwerky, R.P. Klose, P. Vierneisel, G. Bastery, Fibrin glue for reanastomosis of the fallopian tube in the rabbit: Adhesions and fertility, *Human Reprod.* 7 (1992) 1274.
- [10] J.L. Drury, D.J. Mooney, Hydrogels for tissue engineering: Scaffold design variables and applications, *Biomaterials* 24 (2003) 4337–4351.
- [11] C.F. Guimarães, L. Gasperini, A.P. Marques, R.L. Reis, The stiffness of living tissues and its implications for tissue engineering, *Nat. Rev. Mater.* 5 (2020) 351–370.
- [12] F.J. O'Brien, Biomaterials & scaffolds for tissue engineering, *Mater. Today* 14 (2011) 88–95.
- [13] S. Hollister, Porous scaffold design for tissue engineering, *Nat. Mater.* 4 (2005) 518–524.
- [14] T.M. Freyman, I.V. Yannas, L.J. Gibson, Cellular materials as porous scaffolds for tissue engineering, *Prog. Mater. Sci.* 46 (2001) 273–282.
- [15] Q.L. Loh, C. Choong, Three-dimensional scaffolds for tissue engineering applications: Role of porosity and pore size, *Tissue Eng. Part B-Rev.* 19 (2013) 485–502.
- [16] Ž. Knez, E. Markočič, M. Leitgeb, M. Primožič, M.K. Hrnič, M. Škerget, Industrial applications of supercritical fluids: A review, *Energy* 77 (2014) 235–243.
- [17] L.J.M. Jacobs, M.F. Kemmere, J.T.F. Keurentjes, Sustainable polymer foaming using high pressure carbon dioxide: A review on fundamentals, processes and applications, *Green Chem.* 10 (2008) 731–738.
- [18] D.L. Tomasko, H. Li, D. Liu, X. Han, M.J. Wingert, L.J. Lee, K.W. Koelling, A review of CO₂ applications in the processing of polymers, *Ind. Eng. Chem. Res.* 42 (2003) 6431–6456.
- [19] A.R.C. Duarte, J.F. Mano, R.L. Reis, Supercritical fluids in biomedical and tissue engineering applications: A review, *Int. Mater. Rev.* 54 (2009) 214–222.
- [20] R.A. Quirk, R.M. France, K.M. Shakesheff, S.M. Howdle, Supercritical fluid technologies and tissue engineering scaffolds, *Curr. Opin. Solid St. M.* 8 (2004) 313–321.
- [21] L.M. Mathieu, M.O. Montjovent, P.E. Bourban, D.P. Pioletti, J.A.E. Månson, Bioresorbable composites prepared by supercritical fluid foaming, *J. Biomed. Mater. Res. A* 75 (2005) 89–97.
- [22] D.J. Mooney, D.F. Baldwin, N.P. Suh, J.P. Vacanti, R. Langer, Novel approach to fabricate porous sponges of poly (D, L-lactic-co-glycolic acid) without the use of organic solvents, *Biomaterials* 17 (1996) 1417–1422.
- [23] M.-O. Montjovent, L. Mathieu, B. Hinz, L.L. Applegate, P.-E. Bourban, P.-Y. Zambelli, J.-A. Månson, D.P. Pioletti, Biocompatibility of bioresorbable poly (L-lactic acid) composite scaffolds obtained by supercritical gas foaming with human fetal bone cells, *Tissue Eng.* 11 (2005) 1640–1649.
- [24] J.J.A. Barry, H.S. Gidda, C.A. Scotchford, S.M. Howdle, Porous methacrylate scaffolds: supercritical fluid fabrication and *in vitro* chondrocyte responses, *Biomaterials* 25 (2004) 3559–3568.
- [25] H. Li, T.K. Sinha, J.S. Oh, J.K. Kim, Soft and flexible bilayer thermoplastic polyurethane foam for development of bioinspired artificial skin, *ACS Appl. Mater. Inter.* 10 (2018) 14008–14016.
- [26] J. Hou, J. Jiang, H. Guo, X. Guo, X. Wang, Y. Shen, Q. Li, Fabrication of fibrillated and interconnected porous poly(ϵ -caprolactone) vascular tissue engineering scaffolds by microcellular foaming and polymer leaching, *RSC Adv.* 10 (2020) 10055–10066.
- [27] T.P. Haider, C. Völker, J. Kramm, K. Landfester, F.R. Wurm, Plastics of the future? The impact of biodegradable polymers on the environment and on society, *Angew. Chem. Int. Ed.* 58 (2019) 50–62.
- [28] R. Muthuraj, M. Misra, A.K. Mohanty, Biodegradable compatibilized polymer blends for packaging applications: A literature review, *J. Appl. Polym. Sci.* 135 (2018) 45726.
- [29] F.V. Ferreira, L.S. Cividanes, R.F. Gouveia, L.M. Lona, An overview on properties and applications of poly (butylene adipate-co-terephthalate)-PBAT based composites, *Polym. Eng. Sci.* 59 (2019) 7–15.
- [30] J. Song, J. Mi, H. Zhou, X. Wang, Y. Zhang, Chain extension of poly (butylene adipate-co-terephthalate) and its microcellular foaming behaviors, *Polym. Degrad. Stab.* 157 (2018) 143–152.
- [31] J.P. Eubeler, M. Bernhard, T.P. Knepper, Environmental biodegradation of synthetic polymers II. Biodegradation of different polymer groups, *Trends Anal. Chem.* 29 (2010) 84–100.
- [32] A.R. Bagheri, C. Laforsch, A. Greiner, S. Agarwal, Fate of so-called biodegradable polymers in seawater and freshwater, *Global Challenges* 1 (2017) 1700048.
- [33] L.S. Nair, C.T. Laurencin, Biodegradable polymers as biomaterials, *Prog. Polym. Sci.* 32 (2007) 762–798.
- [34] J.M. Anderson, M.S. Shive, Biodegradation and biocompatibility of PLA and PLGA microspheres, *Adv. Drug Delivery Rev.* 64 (2012) 72–82.
- [35] R.A. Jain, The manufacturing techniques of various drug loaded biodegradable poly (lactide-co-glycolide) (PLGA) devices, *Biomaterials* 21 (2000) 2475–2490.
- [36] B. Tesfamariam, Bioresorbable vascular scaffolds: Biodegradation, drug delivery and vascular remodeling, *Pharmacol. Res.* 107 (2016) 163–171.
- [37] A.M. Reed, D.K. Gilding, Biodegradable polymers for use in surgery–poly (glycolic)/poly (lactic acid) homo and copolymers: 2. *In vitro* degradation, *Polymer* 22 (1981) 494–498.
- [38] E.J. Frazza, E.E. Schmitt, A new absorbable suture, *J. Biomed. Mater. Res.* 5 (1971) 43–58.
- [39] J. Zhang, L. Luo, S. Lyu, J. Schley, B. Pudil, M. Benz, A. Buckalew, K. Chaffin, C. Hobot, R. Sparer, Spontaneous transesterification reactions between poly

- (lactide-co-glycolide) and poly (trimethylene carbonate) at the interface, *J. Appl. Polym. Sci.* 117 (2010) 2153–2158.
- [40] C.-X. Chen, Q.-Q. Liu, X. Xin, Y.-X. Guan, S.-J. Yao, Pore formation of poly(ϵ -caprolactone) scaffolds with melting point reduction in supercritical CO₂ foaming, *J. Supercrit. Fluids* 117 (2016) 279–288.
- [41] L. Wang, H. Zhou, X. Wang, J. Mi, Evaluation of nanoparticle effect on bubble nucleation in polymer foaming, *J. Phys. Chem. C* 120 (2016) 26841–26851.
- [42] L.J. White, V. Hutter, H. Tai, S.M. Howdle, K.M. Shakesheff, The effect of processing variables on morphological and mechanical properties of supercritical CO₂ foamed scaffolds for tissue engineering, *Acta Biomater.* 8 (2012) 61–71.
- [43] J.J. Stangel, J.V. Reyniak, M.L. Stone, Conservative surgical management of tubal pregnancy, *Obstet. Gynecol.* 48 (1976) 241–244.
- [44] M.K. Rajendran, Tubal recanalisation-microsurgical tubal reversal anastomosis, *Int. Surg. J.* 5 (2018) 3873–3876.
- [45] I. Gerçek, R.S. Tıgılı, M. Gümüşderelioglu, A novel scaffold based on formation and agglomeration of PCL microbeads by freeze-drying, *J. Biomed. Mater. Res. A* 86A (2007) 1549–3296.
- [46] L.J. Gibson, M.F. Ashby, Cellular solids: structure and properties, Cambridge University Press, Cambridge, 1997.
- [47] R.M. Borland, J.D. Biggers, C.P. Lechene, M.L. Taymor, Elemental composition of fluid in the human fallopian tube, *J. Reprod. Fertil.* 58 (1980) 479–482.
- [48] H.J. Leese, J.I. Tay, J. Reischl, S.J. Downing, Formation of fallopian tubal fluid: role of a neglected epithelium, *Reproduction* 121 (2001) 339–346.
- [49] C.E. Holy, S.M. Dang, J.E. Davies, M.S. Shoichet, *In vitro* degradation of a novel poly (lactide-co-glycolide) 75/25 foam, *Biomaterials* 20 (1999) 1177–1185.
- [50] J. Zhang, B. Xie, Z. Xia, L. Zhao, L. Cen, Y. Yang, A comparable study of polyglycolic acid's degradation on macrophages' activation, *Mat. Sci. Eng. C* 109 (2020) 110574.