Dipyridamole-loaded biodegradable PLA nanoplatforms as coatings for cardiovascular stents

V Bakola1,2, V Karagkiozaki1,2, A R Tsiapla1, F Pappa1, I Moutsios1, E Pavlidou3 and S Logothetidis1

1 Nanotechnology Lab LTFN (Lab for Thin Films—Nanobiomaterials—Nanosystems—Nanometry) Aristotle University of Thessaloniki, 54124, Thessaloniki, Greece
2 BL Nanobiomed P.C. Thessaloniki, Greece
3 Department of Physics, Aristotle University of Thessaloniki, 54124, Thessaloniki, Greece

E-mail: vempakol@physics.auth.gr

Received 30 December 2017, revised 19 March 2018
Accepted for publication 9 April 2018
Published 4 May 2018

Abstract
Cardiovascular stents are commonly used for the treatment of cardiovascular diseases that in developed societies are the most frequent causes of mortality and morbidity. In recent years, thorough research and development of drug-eluting stents has been done, with emphasis on coronary stenting to avoid the most common complication, in-stent thrombosis. Dipyridamole (DPM) is a medication that inhibits blood clot formation. Drug delivery nanoplatforms consisting of biodegradable polymers can be fabricated via electrospinning deposition, known for its cost-effective and versatile advantages, that produces fibrous scaffolds that are able to sustain and control drug release. A novel drug delivery nanosystem of polylactic acid fibrous scaffold loaded with the anti-platelet drug DPM was fabricated by electrospinning as coating for cardiovascular stents. The surface morphology and topography that were evaluated via atomic force microscopy, scanning electron microscopy and optical microscopy, were found to be good and suitable for tissue engineering. Contact angle measurements established the hydrophobic behavior of these fibrous nanoplatforms. Drug-release kinetics and degradation studies were conducted and revealed a sustained and controllable release of DPM, through this fibrous matrix over time. Finally, cytotoxicity studies took place to evaluate the cytocompatibility of the scaffold that confirmed its compatible behavior. The successful performance of this nanoplatform can lead to it being a valuable tool for atherosclerosis treatment.

Keywords: electrospinning, polylactic acid, dipyridamole, cardiac diseases, tissue engineering

Introduction

One of the major and most frequent causes of mortality and morbidity in developing countries, according to the World Health Organization, is cardiovascular diseases and the underlying process of atherosclerosis, a chronic and progressive inflammatory disease that causes endothelial dysfunction and can lead to heart attack or cardiac arrest if untreated [1, 2].

The treatment of coronary heart disease has been revolutionized by the use of arterial stents that act as a supporting scaffold to keep the artery open and maintain the blood flow without obstruction [3]. Also, they assist with terminating the vessel recoil and intimal hyperplasia that are correlated with percutaneous transluminal coronary angioplasty [4].

Nanomedicine offers the opportunity to design new drug delivery systems that can be combined with state-of-the-art
implant technology to create novel and more efficient implants that can release therapeutic agents at the site of the pathogenic area [5, 6]. Therefore, coronary drug-eluting stents (DESs) were developed, as a vehicle of local drug administration, to reduce the possibility of late stent thrombosis and restenosis that are the most common drawbacks of stenting [7–9].

Biodegradable fibrous nanoplastics that act as coatings in the formation of DESs, can be fabricated through a versatile and cost-effective, top down approach, the electrospinning deposition method, that creates 3D scaffolds of various sizes and shapes [10]. Electrospinning uses electrostatic forces to produce nanodimension fibers from polymer solutions or melts [11].

These polymers, which are used in the electrospinning process, are breaking new ground in the pharmaceutical industry as matrices for drug delivery applications [12]. Poly(D, L-lactide) (PDLLA) is one of the most promising biodegradable polymers owing to its mechanical, thermoplastic processibility and biological properties, such as biocompatibility and biodegradability [13]. Due to the fact that it can be dissolved in common solvents for processing and degrades through hydrolysis from the body with nontoxic products, it has been widely used in various biomedical applications [14–16].

Biodegradable materials, such as polylactic acid (PLA), as mentioned above, have proved to be potential stent materials for drug loading systems. The coating acts as a drug storage from which the drug is released in a controlled manner onto the site of inflammation after the implantation [17]. To combat DES late thrombosis, with a mechanism suggested to be the platelet activation and inflammatory reaction of the vessel wall associated with DES [18], the use of anti-thrombotic and anti-platelet drugs is recommended [19].

A pharmaceutical agent that has been used, repeatedly, in patients who are in danger of secondary stroke, is dipyridamole (DPM) due to its anti-thrombotic effect. It is regularly used in combination with acetylsalicylic acid [20]. Research has shown that DPM inhibits both platelet aggregation and thrombus formation in humans [21]. The action of DPM is to inhibit equilibrative nucleotide transporters with the resultant inhibition of the uptake of extracellular adenosine into platelets and also vascular cells. This activates adenosine receptors on the cell surface and increases the intracellular concentration of cyclic adenosine monophosphate [20, 22]. Along with DPM’s anti-oxidative and anti-inflammatory properties, it also inhibits the proliferation of vascular cells, especially smooth muscle cells, and prevents the restenosis of vascular grafts [23].

In this work, with the technical assistance of an electrospinning device and process, biomimetic fibrous scaffolds of PLA, blank and loaded with DPM, were developed to further act as drug delivery coating onto cardiovascular stents. The evaluation of the surface morphology and topography of this drug delivery system was conducted through atomic force microscopy (AFM) and scanning electron microscopy (SEM), as well as optical microscopy and SEM for the coated stent. DPM release from these fibrous matrices, was examined through drug-release kinetics, along with degradation studies, to reveal if the drug release is sustained and controllable over time. Finally, cytotoxicity studies of these scaffolds were carried out, in order to measure the cell viability and validate their cytocompatibility so that they can be used as a safe approach for tissue regeneration applications.

Experimental

Materials and methods

PDLLA (Mw = 75,000–120,000 g mol−1), dichloromethane (DCM) (≥99.8%), dimethylformamide (DMF) (≥99.8%), methanol (≥99.8%) and DPM were the drugs supplied by Sigma-Aldrich. Polymer solutions of PLA with DPM were prepared and electrospun matrices were formed via an electrospinning process (Esprayer™ ES-2000S). Along with AFM (NT—MDT solver, a scanning probe microscope with anti-vibration system MICRO 40 by Halcyonics) and SEM (JOEL, JSM—840A) the morphology and topography of the matrices were evaluated. Phosphate buffer saline (PBS) was also supplied by Sigma-Aldrich. A luminometer (Promega Clomatx Multi Detection System) was used to calculate the drug release and the specimens were preserved in an incubator (Galaxy 1705), dried in a fume cupboard (Telstar PV—30/70) and weighed in a scale (Kern & Sohn GmbH sealed ABT 120—5DM). Blank and DES morphology was examined also with SEM and a Keithley optical microscope (Cascade Microtech). For cytotoxicity studies, mice fibroblasts (L929) were used and the following reagents: methanol (≥99.8%), ethanol (≥99.8%), glutaraldehyde, trypsin, methylene blue, PBS, Dulbecco’s modified eagle medium, 10% fetal bovine serum and 1% antibiotic, which were also supplied by Sigma-Aldrich. A cardiovascular Co/Ni stent was also used.

Experimental

Polymer solution preparation

PLA (MW = 75,000–120,000 g mol−1) was dissolved in a mixture of solvents, such as DMF:DCM. The solution was stirred with a magnetic stirrer overnight until it became homogeneous. Then, DPM was dissolved in methanol, the solution was stirred with vortex for 3 min and it was added to the PLA solution. Specifically, there was a blending of DPM solution with PLA solution and stirred with vortex to become a united solution.

Electrospinning setting and process

Electrospinning uses electrostatic forces to produce thin fibers in nanoscale from a polymeric solution. A DC voltage of several tens of kV is needed to electrically charge the surface of the polymeric solution that is added in a glass syringe in
the device. As the voltage increases, a Taylor cone is formed, which is a charged polymeric solution in a conical shape. At a threshold, when repulsive electrical forces overcome surface tension forces, a jet of nanofibers emerges from the tip of the syringe to the conductive collector. The typical setup of the electrospinning device basically consists of three major components. The feeding unit (e.g. glass syringe), high-voltage power supply (10–30 kV) and a grounded collecting plate (usually a metal screen that can be covered with aluminum foil).

The electrospinning process is conducted at room temperature under atmospheric conditions. All operations are computer-controlled and easy to handle. A laser and a video microscope are used to depict the state of spray on a computer screen. The scan movement of the XY stage and two or three nozzles (maximum) enable it to deposit fast and homogeneously on the deposition board (200 mm × 200 mm).

First, blank PLA solution and then PLA:DPM blend were placed in a glass syringe, the electrospinning process took place and a PLA and a PLA:DPM scaffold were developed onto aluminum foil for further characterization. Then, electrospinning deposition of the PLA:DPM solution was also performed onto a stent sample, for the fabrication of the PLA:DPM scaffold as a drug-eluted coating onto the implant and it was also characterized.

**Characterization of the scaffolds and stent**

AFM and SEM were used for the topography and morphology evaluation of all scaffolds. The detailed structure of each polymeric fibrous mat was imaged by these two methods from (1 × 1 cm) samples. The average fiber diameter was measured from the SEM images using the ImageJ program. The scaffold onto the implant was also characterized with SEM imaging and the Keithley optical microscope so that it could be possible to observe its morphology and whether the deposition and scaffold adhesion were adequate to completely cover it.

**Scaffold degradation over time**

Degradation study took place, in order to evaluate how blank PLA scaffolds and drug-loaded PLA scaffolds degrade through hydrolysis to their components, over time. Scaffold samples (1 × 1 cm) of PLA and PLA:DPM were submerged in PBS solution in well plates and degradation study took place for 3 months to examine how blank and drug-loaded scaffolds degraded over time. The specimens were examined on different days, as they were separated into 24-well plates. They were preserved in an incubator, and on specific days, the PBS solution was removed, the scaffold samples were dried in a fume cupboard and weighed in a scale to measure their mass before and after the PBS addition according to the equation:

\[
\text{Degradation} = \frac{(W_T - W_o)}{W_T} \cdot 100.
\]

**Drug-release study of drug-loaded scaffolds**

Drug-release study was conducted to indicate how the drug is released from the drug-loaded scaffold over time. Scaffold samples (1 × 1 cm) of PLA:DPM were also submerged in well plates with PBS solution in order to examine the drug-release kinetics over time. During the first 24 h, burst release took place, as on the first day the extraction of the drugs is very high, so six solution samples were taken. Then at standard days, samples of the PBS solution with the released drug were taken and were placed in 96-well plates. The specimens were preserved in an incubator at 37°C and a luminometer was used to calculate the drug’s absorption, the release of the drug and its kinetics. The procedure is accumulative, so each measurement was added to the previous to obtain a drug-release diagram.

**Cytotoxicity studies of the scaffolds**

In order to examine cytocompatible or toxic behavior of the fabricated fibrous scaffolds, three methods of cytotoxicity were implemented and the cells that were used were mice fibroblasts (L929). First, MTT assay, a biochemical and quantitative method, was used to measure the cell viability of the scaffold samples, in comparison with the cell viability of the control that contained only cells. MTT protocol was performed and samples of the solution were taken and inserted into 96-well plates for day 1, 3 and 5. A luminometer was used to calculate the absorption of tetrazolium crystals, so as to obtain the comparison diagram of PLA, and PLA:DPM with the control sample. Quantitative and qualitative methods of methylene blue and SEM imaging were also used as cytotoxicity studies, in order to observe the morphology and allocation of the cells onto and into the scaffolds and how the cells adhere, grow and proliferate for day 1, 3 and 5 onto the surface of the fibrous scaffolds and/or into them. The process of these methods was performed on the fibrous scaffolds and the samples were maintained in the incubator. Cytotoxicity results reveal the adequacy of these scaffolds to be validated candidates for tissue regeneration use.

**Results and discussion**

**Surface characterization of the PLA and PLA:DPM scaffolds**

With the assistance of the electrospinning method, PLA scaffolds were fabricated with good and dense morphology without beads, as observed and validated from their characterization with AFM and SEM measurements. The AFM images were edited with the program NOVA. Peak-to-peak and root mean square roughness was measured at 1.917 and 342 nm, respectively (figure 1). The average diameter of 20 random fibers, taken from the SEM image of the specimen was calculated with the ImageJ program, at 522 nm. The obtained diagram of the amplitude of the fibers shows the diameter of the fibers versus the multitude of the fibers (figure 2).
Contact angle measurements were conducted in order to evaluate the hydrophobic or hydrophilic behavior of the scaffold, and as shown in figure 3, the PLA scaffold is hydrophobic with partial wetting and a mean contact angle of $124.9^\circ \pm 0.4$.

After blending the PLA and DPM solutions, also through electrospinning deposition, drug-loaded scaffolds were fabricated with good, dense morphology without beads. The characterization of the scaffolds was also made via AFM and SEM measurements. The peak-to-peak and root mean square roughness from the AFM images were 1.188 and 251 nm, respectively (figure 4). The SEM images show a good mesh of fibers as well, and the average fiber diameter was calculated at 556 nm (figure 5).

The roughness of the surface is an important parameter, as it determines cell growth in cytotoxicity studies. Cells need an anomalous surface to grow and nanofibrous scaffolds are suitable for this purpose. Both scaffolds have great roughness that favors cell adhesion and growth that makes them more cytocompatible.

Contact angle measurements were also conducted at the drug-loaded scaffold, in order to evaluate the hydrophobic or hydrophilic behavior of the scaffold, and to compare it with the blank scaffold’s contact angle and observe how the addition of the drug affected its hydrophobicity. As shown in figure 6, the PLA:DPM scaffold is hydrophobic with partial wetting and a mean contact angle of $129.3^\circ \pm 1.7$.

The contact angle measurements indicate that the PLA:DPM scaffold is even more, although slightly, hydrophobic than the PLA scaffold. With the addition of the drug, as mentioned earlier, the scaffold’s roughness has decreased and
this caused less surface wetting and thus the increase of the contact angle and its hydrophobicity.

**Degradation of the PLA and PLA:DPM scaffolds**

The degradation study of the PLA and PLA:DPM scaffolds took place over 3 months. In this period, it was observed how the scaffolds degrade with hydrolysis to their components, over time, as shown in figure 7. The degradation rate for both scaffolds was low and steady. In 90 d, the PLA scaffolds degraded 25% of their mass and the PLA:DPM scaffolds degraded 38% of their mass (figure 7).

It was observed that after contact of these scaffolds with PBS solution, they detached from the substrate (aluminum foil) and shrunk to a large extent, especially the drug-loaded ones. Their contraction has made them difficult to study, and this was due to the physico-chemical properties of PLA.

PLA polymer is sensitive and it degrades under humid conditions, causing the hydrolysis of ester bonds to reduce the degree of polymerization [24]. According to studies, it has been noted that with the increase of temperature, PLA fibers shrink, which also affects their mechanical properties [25]. The samples in this experiment were kept in the incubator at 37 °C and the environment was warm enough. High crystallinity reduces the shrinkage effect in a warm environment [25]. With the increase of molecular weight, the crystallinity of the polymer decreases. The PLA that was used had high molecular weight and hence low crystallinity, thus resulting in high shrinkage.

All the above led to the shrinkage of these scaffolds, which although hydrophobic, shrank and degraded to a large extent from the very first day of degradation, as shown below in the SEM images for the first day of their degradation study, particularly for scaffolds that contained the drug (figures 8, 9).
A comparison of both scaffolds, blank and drug loaded, was made through SEM images that depict how the scaffolds slowly degraded by the 1st, 30th and 90th day. In addition, diagrams with the amplitude of fiber diameter were calculated with the program ImageJ to obtain the average fiber diameter of these days of degradation. It is observed in figures 8 and 9 that the average fiber diameter increased in 30 d and then decreased in 90 d for both scaffolds, blank and drug loaded. For the PLA scaffolds the average diameter on the 1st day was 426 nm, on the 30th day 616 nm and on the 90th day 477 nm. For the PLA:DPM scaffold the average diameter on the 1st day was 602 nm, on the 30th day 951 nm and on the 90th day 415 nm, as shown in table 1.

In both scaffolds, their fiber diameter increased in 30 d, due to swelling of the scaffold, along with the hydrophobic behavior of PLA. Then, in 90 d the degradation of the polymer took place and it started to decompose due to hydrolysis, therefore their diameter decreased due to degradation of the scaffold.

The swelling of the fibers is a result of PBS absorption along with the hydrophobicity of the polymer that cause fibers and in extension the whole scaffold to expand before substantial degradation takes place. In tissue engineering, swelling behavior is an important factor, which influences the chemical and physical characteristics of the scaffolds after and prior to implantation [26].

**Drug-release kinetics of the PLA:DPM scaffolds**

The pharmacokinetics of the PLA:DPM scaffolds lasted almost 7 months. Figure 10 shows the diagram of the PLA:DPM pharmacokinetics. It is a triphasic release pattern that
shows the initial burst of the drug after the first 24 h, which is 13% DPM release. Then, the release became slow and controlled and in a 182 d period accounted for 82% of the total DPM loading. Finally, in 218 d, a total drug release occurred and 100% of the drug was released through the scaffolds. In the diagram, in the first 24 h, burst-release diffusion can be observed where the drug release is very intense, then the decay of the polymeric matrix occurs where the drug release is controlled and steady and in the end the lag phase, where the drug release is very low and slow.

Cytotoxicity studies of the PLA and PLA:DPM scaffolds

Cytotoxicity studies took place on these scaffolds in order to validate their cytocompatibility, so they can be safely used for regenerative medical applications, such as stent coatings. MTT assay, compared cell viability between blank, DPM-loaded PLA scaffolds and the control sample that contained only cells. The results that are demonstrated in the diagram in figure 11 show that both scaffolds’ cell viability was more than the control sample for all experiment periods (1, 3 and 5 d), so as to determine their cytocompatibility and to show that they are not toxic to the cells. The decline of cell viability on day 5 in both scaffolds possibly occurred because sometimes cells may overflow the scaffolds and due to the fact that the L929 cell cycle is short (5 d). Also, DPM inhibits cell proliferation and contributes to cell cycle progression and the induction of apoptosis in cells [18]. Overall, the cell viability of all scaffolds and for all experiment days was more than the control sample and this confirms their cytocompatible behavior. With methylene blue and SEM images, cell adhesion, growth and proliferation for day 1, 3 and 5 onto the surface and/or into the fibers of the scaffolds, can be observed until they cover the scaffold surface on day 5 (figures 12, 13).

From methylene blue images (figure 12), the staining of cell nuclei provide better observation and quantification on the scaffolds. There is a gradual quantitative growth and proliferation of the cells over the course of the days in both scaffolds. In particular, on day 5 the cells covered almost the entire surface of both scaffolds and it can be clearly seen that their surfaces were filled with cells. In conclusion, both fibrous polymer scaffolds appear to be cytocompatible, since they favor cell viability.

From the SEM images (figure 13), it can also be noted that cell growth has been favored in both scaffolds, and cells appear to grow and proliferate on their surface over the course of the days (1, 3, 5), with a little less cell growth at the drug-loaded scaffold. As mentioned above, this is due to the increased roughness of the PLA scaffold rather than that of the drug-loaded one, which favors the growth and proliferation of the cells.

Together, these two fabricated nanoplatforms are suitable for cellular growth, making them useful as biomaterials in tissue regeneration.

Table 1. Average fiber diameter over time for the PLA and PLA:DPM scaffold degradation.

| Days | PLA   | PLA:DPM |
|------|-------|---------|
| 1    | 426   | 602     |
| 30   | 616   | 951     |
| 90   | 477   | 415     |

Figure 9. (A), (D) PLA:DPM scaffold degradation for the 1st day, amplitude of fibers; (B), (E) for the 30th day, amplitude of fibers; (C), (F) for the 90th day, amplitude of fibers. (A)–(C) x500, (D)–(F) x3000.
Through the electrospinning process of the PLA:DPM solution, a PLA:DPM scaffold was deposited onto a cardiovascular Co/Ni stent. Its morphology was examined with a Keithley optical microscopy that has great resolution, and SEM images. Very good scaffold morphology onto the stent was achieved, with a good and dense mesh of fibers. The adhesion onto the stent was sufficient, as observed from the following images (figure 14).

The PLA:DPM scaffold was so dense that a cocoon-like coating formed over the stent’s surface, although the electrospinning process took place for only 5 min.

Furthermore, the mechanical properties of these fabricated scaffolds can also be assessed to compare the difference without and with the addition of the drug into the polymer. Upon completion of the in vitro experiments, in vivo studies of these polymeric scaffold-coated implants can be conducted in the future, to examine their viability in living organisms.

Conclusions

In this work, an anti-platelet drug-loaded biodegradable polymer nanoplatform was fabricated via electrospinning deposition, to perform as a drug-eluting coating onto...
cardiovascular stents, and help to cope with artery thrombosis that often occurs after stent implantation.

The scaffolds that were developed, with characterization performed via AFM and SEM measurements, exhibited very good morphology and topography, with a good and dense mesh of fibers without beads, which resembles extracellular matrix and promotes neointimalization after surgery. It was observed through SEM images that the diameter of the fiber thickens with the addition of the drug. This means that the drug is inserted entirely and throughout the polymer, so its release will be homogeneous as the drug-loaded scaffold degrades. As the scaffold degrades, the diameter of the fibers initially increases due to swelling and then decreases over time due to degradation, in both scaffolds. This shows that as the polymer degrades over time, the drug is released in a controllable way. Drug-release kinetics, in line with degradation studies revealed a sustained and controllable release of the DPM drug, through fibrous matrices over time.

**Figure 12.** Cell staining with methylene blue of the fibrous polymeric scaffold: (A)–(C) PLA and (D)–(F) PLA:DPM, for quantitative analysis of the L929 cell proliferation for days 1, 3 and 5.

**Figure 13.** SEM images of the L929 cell proliferation on the fibrous polymeric scaffold: (A)–(C) PLA and (D)–(F) PLA:DPM, on days 1, 3 and 5, to study their cytocompatibility.
Cytotoxicity studies confirmed the cytocompatible behavior of this nanoplatform as suitable for tissue engineering and the deposition onto the stent was successful and thorough.

The felicitous fabrication of this fiber-based nanoplatform that encapsulates an anti-platelet drug, along with the unparalleled morphology and topography, provides properties that control the drug pharmacokinetics in vitro. In conclusion, the implementation of this useful nanoplatform could break new ground in antithrombotics and amend the treatment of atherosclerosis.

Acknowledgments

This work has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement 646222, NanoReg II project.

ORCID iDs

V Bakola @ https://orcid.org/0000-0002-0771-0756

References

[1] Karagkiozaki V, Logothetidis S and Pappa A-M 2015 Nanomedicine for atherosclerosis: molecular imaging and treatment J. Biomed. Nanotechnol. 11 191–210

[2] Pappa A M et al 2015 Oxygen-plasma-modified biomimetic nanofibrous scaffolds for enhanced compatibility of cardiovascular implants Beilstein J. Nanotechnol. 6 254

[3] McGinty S 2014 A decade of modelling drug release from arterial stents Math. Biosci. 257 80–90

[4] Zilberman M and Eberhart R C 2006 Drug-eluting bioresorbable stents for enhanced compatibility of cardiovascular implants Beilstein J. Nanotechnol. 6 254

[5] Karagkiozaki V et al 2012 Development of a nanoporous and multilayer drug-delivery platform for medical implants Int. J. Nanomed. 7 5327

[6] Tsiapla A R et al 2017 Drug delivery nanosystems for cardiovascular stents Mater. Today 4 6869–79

[7] Kurecic M and Smole M S 2013 Electrospinning: nanofibre production method Tekstilec 56 4–12

[8] Gupta B, Revagade N and Hilborn J 2007 Poly(lactic acid) fiber: an overview Prog. Polym. Sci. 32 455–82

[9] Kim K et al 2003 Control of degradation rate and hydrophilicity in electrospun non-woven poly (D, L-lactide) nanofiber scaffolds for biomedical applications Biomaterials 24 4977–85
[15] Elsawy M A et al 2017 Hydrolytic degradation of polylactic acid (PLA) and its composites Renew. Sustain. Energy Rev. 79 1346–52
[16] Qi Y et al 2018 Strategy of metal-polymer composite stent to accelerate biodegradation of iron-based biomaterials ACS Appl. Mater. Interfaces 10 182–92
[17] Uurto I et al 2005 Drug-eluting biodegradable poly-D/L-lactic acid vascular stents: an experimental pilot study J. Endovasc. Ther. 12 371–9
[18] Karagkiozaki V C et al 2010 Nanomedicine for the reduction of the thrombogenicity of stent coatings Int. J. Nanomed. 5 239
[19] Rhee J-W and Wu J C 2013 Advances in nanotechnology for the management of coronary artery disease Trends Cardiovascular Med. 23 39–45
[20] Repanas A et al 2016 The effect of dipyridamole embedded in a drug delivery system made by electrospun nanofibers on aortic endothelial cells J. Drug Deliv. Sci. Technol. 35 343–52
[21] Singh J P et al 1994 Dipyridamole directly inhibits vascular smooth muscle cell proliferation in vitro and in vivo: implications in the treatment of restenosis after angioplasty J. Am. Coll. Cardiol. 23 665–71
[22] Brown D G, Wilkerson E C and Love W E 2015 A review of traditional and novel oral anticoagulant and antiplatelet therapy for dermatologists and dermatologic surgeons J. Am. Acad. Dermatol. 72 524–34
[23] Zhuplatov S B et al 2006 Mechanism of dipyridamole’s action in inhibition of venous and arterial smooth muscle cell proliferation Basic Clin. Pharmacol. Toxicol. 99 431–9
[24] Ma M and Zhou W 2015 Improving the hydrolysis resistance of poly (lactic acid) fiber by hydrophobic finishing Ind. Eng. Chem. Res. 54 2599–605
[25] Jamshidian M et al 2010 Poly-lactic acid: production, applications, nanocomposites, and release studies Compr. Rev. Food Sci. Food Saf. 9 552–71
[26] Nazemi K et al 2014 Synthesis and characterization of poly (lactic-co-glycolic) acid nanoparticles-loaded chitosan/bioactive glass scaffolds as a localized delivery system in the bone defects BioMed Res. Int. 2014 898930