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Original Article

Antibacterial activity of ciprofloxacin-impregnated 3D-printed polylactic acid discs: an in vitro study

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Abstract

Introduction: Three-dimensional (3D) printing technology allows incorporation of various substances including antibiotics into different structures. This study aimed to evaluate the antibacterial activity of ciprofloxacin-impregnated 3D discs against *Escherichia coli*.

Methodology: Polylactic acid pellets were coated with ciprofloxacin at 1% and 2% concentrations, then filaments were produced from these pellets, and antibiotic-containing discs were obtained using fused deposition modeling 3D printers. The working temperatures during filament extrusion and 3D printing processes were 200 °C and 215 °C, respectively. Therefore, in order to test the thermal stability of ciprofloxacin during these processes, the antibiotic was exposed to 200 °C and 215 °C in an oven, and then tested against *E. coli*. Following this, efficiencies of antibiotic-coated pellets, filaments and discs against *E. coli* were determined by diffusion tests.

Results: Ciprofloxacin heated at 200 °C and 215 °C was stable and retained its antibacterial activity. Pellets, filaments and discs coated with 1% or 2% concentration of ciprofloxacin produced inhibition zones in the culture plates. Increasing ciprofloxacin concentration did not significantly affect the diameter of inhibition zones ($p > 0.05$). Ciprofloxacin-containing polylactic acid pellets produced significantly larger inhibition zones than those of filaments and discs ($p < 0.0001$). The difference in zone diameters around ciprofloxacin-containing filaments and discs was not statistically significant ($p > 0.05$).

Conclusions: Ciprofloxacin-coated polylactic acid-based 3D discs displayed antibacterial activity against *E. coli*. This suggests that, various polylactic acid-based ciprofloxacin-containing 3D products can be obtained and evaluated for antibacterial activity in future studies.

Key words: Ciprofloxacin; *Escherichia coli*; 3D printing; disc.

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Introduction

In recent years, three-dimensional (3D) printing technology has been a remarkable field in medicine. This technology has a wide-range of applications such as construction of personalized prostheses, implants and anatomical models, bio-production of 3D tissue and organ models and printing of therapeutic agents [1-4]. Bioactive materials can be integrated into the printed products using 3D printing technology. This system also allows incorporation of antibiotics into 3D-printed constructs [5]. Fabrication of antibiotic-impregnated constructs by 3D printing offers various advantages such as personalization of the product, adjusting drug concentration, and increasing antibiotic distribution [5].

Systemic administration of antibiotics can cause adverse reactions. Use of antibiotic-impregnated 3D constructs at the site of infection can allow personalized and patient-specific treatment, and can also reduce the possibility of toxic effects and antibiotic resistance caused by systemic treatment. Clinical application of antibiotic-incorporated 3D constructs also provides additional advantages such as containing biodegradable base materials and having better drug release profiles, compared to conventional antibiotic-impregnated implants [6].

So far, different techniques have been used for 3D printing. Among these, fused deposition modeling (FDM) has been the most common method for production of antibiotic-impregnated 3D products. In the FDM technique, various types of base materials can be used for 3D printing of antibiotic-incorporated constructs [5]. Polylactic acid (PLA) is a biodegradable material and is one of the common polymers used in 3D printing [7-10]. Several studies used PLA as the base material in order to produce antibiotic-impregnated 3D constructs [6,11-14].

In the present study, ciprofloxacin was incorporated into PLA-based materials for 3D printing.

Ciprofloxacin is a second-generation fluoroquinolone antibiotic, which is used for treating a variety of infections. This antibiotic is active against different bacterial species, including *Escherichia coli* [15]. In addition, ciprofloxacin has high melting and degradation temperatures, therefore this antibiotic can remain stable when exposed to high temperatures during extrusion and 3D printing processes [16].

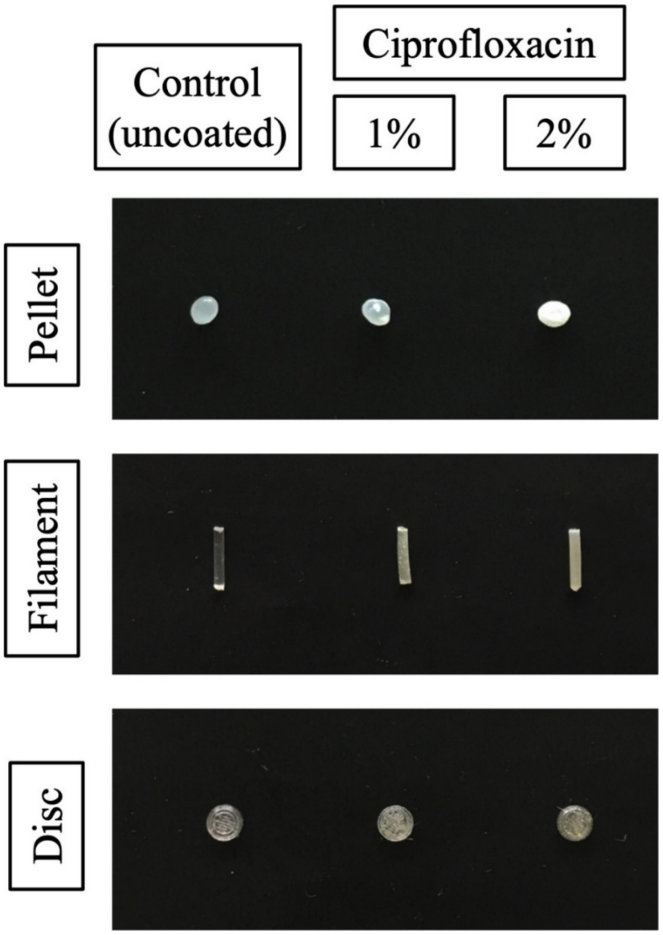
In the light of the above facts, this study aimed to obtain ciprofloxacin-coated 3D-printed discs and evaluate their antibacterial activity against *E. coli*. To achieve this goal, PLA pellets were coated with ciprofloxacin, and filaments were extruded from these materials. Next, antibiotic-coated discs were obtained using 3D printers. Finally, efficiencies of antibiotic-containing pellets, filaments and discs against *E. coli* were evaluated by using diffusion tests.

Methodology

Evaluation of thermal stability of ciprofloxacin

Since ciprofloxacin was to be exposed to high temperatures during filament extrusion (200 °C for 20 minutes) and 3D printing (215 °C for 15 minutes) processes, thermal stability of the antibiotic was tested by ensuring the same conditions in an oven (Jeio Tech, Daejeon, Republic of Korea). First, ciprofloxacin powder (Sigma-Aldrich, St. Louis, USA) was placed in two small glass bottles, and these were kept in the oven at 200 °C for 20 minutes in order to test for thermal stability during the filament extrusion process. Following this, the bottles were brought at room temperature, and one of them was further incubated in the oven at 215 °C for 15 minutes in order to test for thermal stability during the 3D printing process. Then, the antibacterial activity of heated ciprofloxacin, which was exposed to 200 °C only, and both to 200 °C + 215 °C, was tested against *E. coli*. Mueller-Hinton media (Merck, Darmstadt, Germany) were inoculated with a 0.5 McFarland suspension of *E. coli* (ATCC 25922) by using a sterile swab. One milligram from the heated ciprofloxacin powders as well as control (unheated) antibiotic were then placed on the center of the culture plates. All of the tests were performed in five replicates. After incubation at 37 °C for 24 hours, the diameter of the inhibition zone in each plate was measured from three different points. The average of the diameters obtained in five plates was calculated for each set.

Figure 1. Control (uncoated), 1% and 2% ciprofloxacin-coated PLA pellets, filaments and discs.



Coating PLA pellets with ciprofloxacin

For coating of PLA pellets (ColorFabb B.V, Belfeld, Netherlands) with ciprofloxacin (Sigma-Aldrich, St. Louis, USA) the protocol described by Weisman *et al.* [6] was followed with slight modifications. Ciprofloxacin was used at 1% and 2% concentrations for coating of the pellets. For each antibiotic concentration, 20 g of pellets were added into a sterile 50 mL tube. Forty microliters of silicon oil (Sigma-Aldrich, St. Louis, USA) were then added and the tube was vortexed in order to coat the surface of the pellets with the oil. Then the pellets were transferred into a new tube, ciprofloxacin powder was added, and the tube was vortexed vigorously in order to coat the pellets with the antibiotic. In order to obtain 1% and 2% concentrations, 200 mg and 400 mg ciprofloxacin were added to the 20 g pellet containing tubes, respectively. The antibiotic-coated PLA pellets (Figure 1) were then placed into new tubes.

Production of filaments from ciprofloxacin-coated pellets

Filafab filament extruder (D3D Innovations, Bristol, United Kingdom) was used to obtain filaments from the pellets coated with 1% and 2% ciprofloxacin. The working principle of this device is based on the

pellets being collected in a chamber and then pushed into a heated chamber with a screw. When adequate melting is achieved, softened plastic is extruded from the 2.6 mm nozzle. Filament production of the desired diameter is achieved by providing light pull with its pulley system. In this study, the working temperature was kept at 200 °C. Before the addition of pellets coated with 1% and 2% concentrations of the antibiotic, plain PLA pellets were loaded into the machine in order to ensure chamber cleaning and prevent cross contamination. Filament segments of 2 m length and 1.65 - 1.80 mm diameter were used for our study. These filaments were cut into 10 mm length for the diffusion tests (Figure 1). The remaining filaments were used for 3D printing of the discs.

3D printing of ciprofloxacin-impregnated discs

Antibiotic disc models of 6 mm diameter and 1 mm height were used for printing. Tinkercad software (Autodesk Inc, California, USA) was used to design the 3D models. The models were sliced in ".stl" format with the Prusa Slicer software (Prusa Research, Prague, Czechia) for 3D printing. Printing was done with the following parameters: Temperature 215 °C, 20% rectilinear infill, and 0.2 mm layer height. Filaments with appropriate working diameter (1.65 - 1.80 mm) were loaded to Prusa I3 MK3 3D printer (Prusa Research, Prague, Czechia), and 3D printing was done. In order to prevent cross contamination within the machine, discs containing 1% and 2% concentrations of the antibiotic (Figure 1) were printed on different devices.

Antibiotic susceptibility tests

Antimicrobial effects of antibiotic-coated pellets, filaments and 3D discs were determined by diffusion tests. *E. coli* (ATCC 25922) suspension at 0.5 McFarland standard was inoculated onto Mueller-Hinton media (Merck, Darmstadt, Germany) with a sterile swab. Then ciprofloxacin-containing pellets, filaments (10 mm long and 1.75 mm in diameter) or discs (6 mm in diameter and 1 mm in height) were placed on the center of the media. Diffusion tests were performed for both 1% and 2% ciprofloxacin. All the tests were performed in five replicates. A pellet, a filament, and a disc without any antibiotic was used as control and tested in the Mueller-Hinton plates inoculated with *E. coli*. The culture plates were evaluated after an incubation period of 24 hours at 37 °C. Diameter of inhibition zone formed around the antibiotic-containing material in each plate was measured from three different points. The average of the diameters obtained in five plates was calculated for each set.

Statistical analysis

In order to compare the diameters of inhibition zones, firstly, Descriptive statistics were calculated for each group. Data were represented as arithmetic mean ± standard deviation, and median (minimum - maximum). Kruskal-Wallis test was used to compare the inhibition zone diameters generated following thermal stability test. Two-way ANOVA test was performed to determine the effects of material type (pellet, filament and disc) and ciprofloxacin concentration (1% and 2%) on the diameter of the inhibition zones generated in the antibiotic susceptibility tests. Following a statistically significant result, Sidak's multiple comparison test was applied to investigate pairwise differences. Level of significance was accepted to be 0.05. All calculation and analysis were performed with GraphPad Prism 8 for MacOS (Demo Version 8.2.1).

Results

Thermal stability of ciprofloxacin

Ciprofloxacin was heated in an oven at high temperature and thermal stability of the heated antibiotic was evaluated by the diffusion test. In order to compare the antimicrobial activity of heated ciprofloxacin against *E. coli*, control (unheated) antibiotic was also tested. Unheated ciprofloxacin produced inhibition zones that averaged 40.80 ± 1.64 mm [median: 40.00 (39.00 - 43.00) mm]. Ciprofloxacin heated at 200 °C for 20 minutes had inhibition zones averaging 40.40 ± 3.65 mm [median: 40.00 (35.00 - 45.00) mm]. Ciprofloxacin heated at 200 °C for 20 minutes and then exposed to 215 °C for 15 minutes had inhibition zones that averaged 38.20 ± 1.30 mm [median: 38.00 (37.00 - 40.00) mm]. Statistical analysis found no significant difference between zone diameters of the three groups (p = 0.112) (Table 1 and Figure 2).

Table 1. Diameters of inhibition zones generated following the thermal stability test.

Ciprofloxacin (1 mg)	Diameter of inhibition zones (mm)		
	Mean ± SD	Median (min - max)	*p* value
Control (unheated)	40.80 ± 1.64	40.00 (39.00 - 43.00)	0.112
Heated (200 °C, 20 minutes)	40.40 ± 3.65	40.00 (35.00 - 45.00)	
Heated (200 °C, 20 minutes + 215 °C, 15 minutes)	38.20 ± 1.30	38.00 (37.00 - 40.00)	

Figure 2. Box plots showing the diameters of inhibition zones generated by the control (unheated) and heated ciprofloxacin ($p = 0.112$).

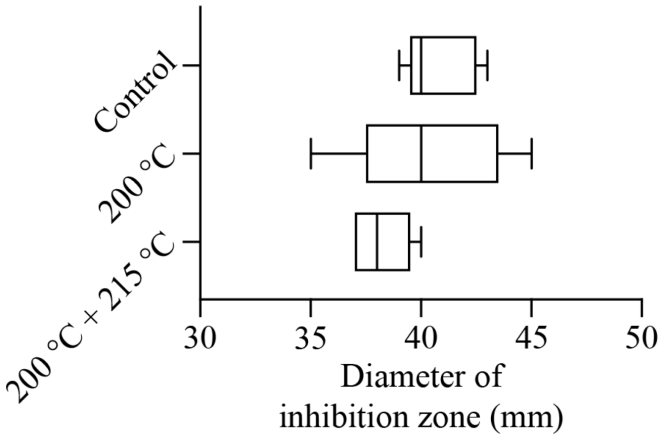


Figure 3. Inhibition zones generated by the control (unheated) and heated ciprofloxacin in the culture plates inoculated with *Escherichia coli*.

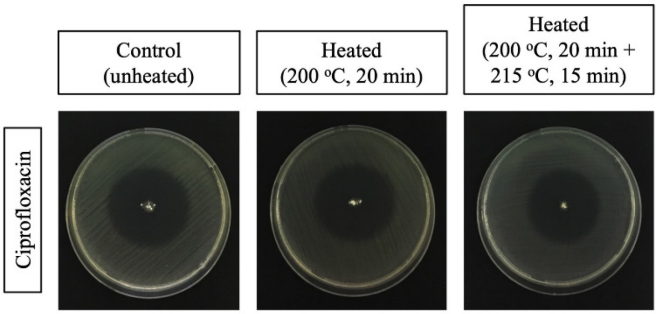


Figure 4. Test results of control (uncoated), 1% and 2% ciprofloxacin-coated PLA pellets, filaments and discs in the culture plates inoculated with *Escherichia coli*.

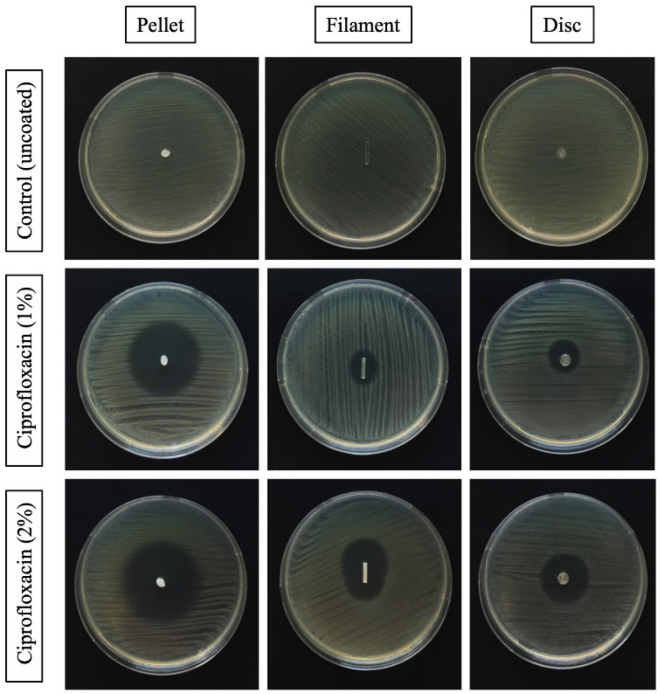
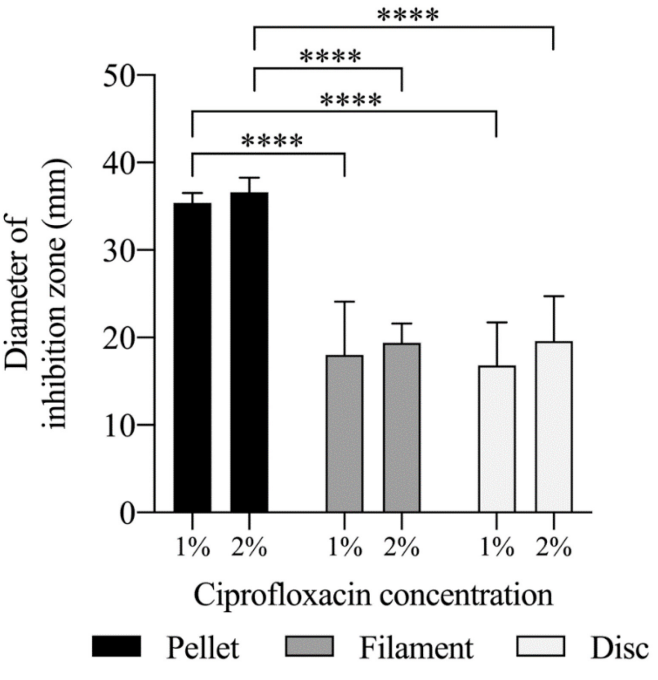


Figure 5. Bar charts showing the diameters of inhibition zones generated by 1% and 2% ciprofloxacin-coated PLA pellets, filaments and discs (**** $p < 0.0001$).



This result indicated that the inhibition zones produced with heated ciprofloxacin were similar to that of the control, and therefore the heated antibiotic retained its antibacterial activity (Figure 3).

Test results of PLA pellets, filaments and 3D discs

Control (uncoated) PLA pellets, filaments and 3D discs that did not contain any antibiotic were tested in the Mueller-Hinton plates. These materials did not produce any inhibition zone in the culture plates. However, PLA pellets, filaments and 3D discs that were coated with 1% or 2% ciprofloxacin had antibacterial effect on *E. coli* and produced inhibition zones in the plates (Figure 4). PLA pellets that contained 1% and 2% ciprofloxacin had inhibition zones averaging 35.40 ± 1.14 mm and 36.60 ± 1.67 mm, respectively. The filaments coated with 1% and 2% ciprofloxacin produced inhibition zones that averaged 18.00 ± 6.12 mm and 19.40 ± 2.19 mm, respectively. Average inhibition zone diameters of 1% and 2% ciprofloxacin-containing 3D discs were 16.80 ± 4.92 mm and 19.60 ± 5.13 mm, respectively. The zone diameters generated by each material were not significantly affected by the concentration of ciprofloxacin ($p > 0.05$). However, the zone diameters generated by antibiotic-coated pellets at both concentrations were significantly higher than those of antibiotic-coated filaments and discs ($p < 0.0001$). Difference between zone diameters of ciprofloxacin-containing filaments and discs was not statistically significant at both concentrations ($p > 0.05$) (Table 2 and Figure 5).

Discussion

Three-dimensional printing is a promising technology in medicine that enables production of customized devices, implants and drugs. This technology provides optimization of the product size, shape and dosage for the patients [16]. Currently many studies in the field of medical 3D printing focus on personalized treatment approaches for drug dosages, drug release systems, patient-specific devices and implants [17]. In a previous study, Muwaffak *et al.* demonstrated effective antibacterial activity of 3D-scanned and 3D-printed patient-specific silver and zinc-impregnated wound dressings [18].

An additional advantage of this technology is the production of antibiotic-coated or impregnated 3D constructs. Site-specific delivery of antibiotic-impregnated 3D-printed products can reduce the adverse effects of systemic treatment, and may also have better drug release from the biodegradable base materials [6]. Antibiotic infused, coated or impregnated implants have been extensively investigated for a long time. Alvarez *et al.* showed that implants produced from PLA, tricalcium phosphate, hydroxyapatite and ciprofloxacin mixture provided reduction in bacterial growth in the experimental osteomyelitis model in rabbits [19]. Qamar *et al.* demonstrated that 3D-printed polypropylene (PP) and polyvinyl alcohol (PVA) hernia meshes which were produced from ciprofloxacin-coated filaments showed 60-70% drug release in the first hour and drug release plateaued 6-7 hours after implantation in experimental rabbit models [20].

Ciprofloxacin is a common antibiotic that is used for the treatment of a variety of infections. Moreover, this antibiotic has high melting and degradation temperatures, which make it thermally stable during the extrusion and 3D printing processes. Saviano *et al.* demonstrated straightforward and effective use of hot melting and subsequent FDM 3D printing of ciprofloxacin-impregnated PVA discs with favorable drug release profiles [16].

In this study, we used an FDM 3D printing technique to produce ciprofloxacin-impregnated discs. PLA pellets were first coated with ciprofloxacin, then the filaments were hot-melt extruded, and finally antibiotic-impregnated discs were 3D printed. In order to test the thermal stability of ciprofloxacin during filament extrusion and 3D printing processes, the antibiotic was treated at high temperatures in an oven. After exposure to 200 °C for 20 minutes and further incubation at 215 °C for 15 minutes, the heated ciprofloxacin produced inhibition zones averaging 40.40 ± 3.65 mm and 38.20 ± 1.30 mm, respectively. The average zone diameter of the control (unheated) antibiotic was 40.80 ± 1.64 mm, and statistical analysis found no significant difference between the zone

Table 2. Diameters of inhibition zones generated by the materials containing 1% and 2% ciprofloxacin.

Antibiotic	Average diameters of inhibition zones (mm) Mean ± SD		
	Pellet	Filament	Disc
Ciprofloxacin (1%)	$35.40 \pm 1.14^{a,A}$	$18.00 \pm 6.12^{b,A}$	$16.80 \pm 4.92^{b,A}$
Ciprofloxacin (2%)	$36.60 \pm 1.67^{a,A}$	$19.40 \pm 2.19^{b,A}$	$19.60 \pm 5.13^{b,A}$

In each row, same lowercase letters indicate no statistically significant difference between groups ($p > 0.05$); different lowercase letters indicate statistically significant difference between groups ($p < 0.05$). In each column, same uppercase letters indicate no statistically significant difference between groups ($p > 0.05$).

diameters of heated and unheated ciprofloxacin ($p > 0.05$) (Table 1, Figure 2 and Figure 3). These findings confirm that the heated antibiotic was still effective against *E. coli* and therefore it was stable at the high temperatures during the filament extrusion and 3D printing processes. These results are consistent with the findings of Weisman *et al.* where gentamicin was used to print antibiotic-coated 3D constructs [6]. In that study, gentamicin was heated at 220 °C for 5 minutes. Activities of heated and control (unheated) gentamicin were tested against *E. coli*. The authors found that heated and control gentamicin produced inhibition zones that averaged 36.61 ± 1.56 mm and 37.39 ± 0.55 mm, respectively [6].

In our study, control (uncoated) PLA pellets, filaments and discs were tested against *E. coli* in order to understand whether these materials had an inhibitory effect on bacterial growth. After the incubation period, no inhibition zone was observed in the culture plates, suggesting that the control materials did not have any antibacterial effect (Figure 4). This result is consistent with the findings of Weisman *et al.* who observed that the uncoated PLA pellets, filaments and discs did not produce any inhibition zone in the culture plates [6].

The effect of antibiotic-coated materials was evaluated by using ciprofloxacin at 1% and 2% concentrations. In the diffusion tests, ciprofloxacin-coated PLA pellets, filaments and discs produced inhibition zones in the culture plates inoculated with *E. coli* (Figure 4). The zone diameters generated by PLA pellets, filaments and discs were not significantly affected by ciprofloxacin concentration ($p > 0.05$). This finding suggests that increasing the antibiotic concentration from 1% to 2% did not significantly improve antibacterial activity of the materials. PLA pellets coated with 1% and 2% ciprofloxacin generated the largest zone diameters averaging 35.40 ± 1.14 mm and 36.60 ± 1.67 mm, respectively. The average inhibition zones produced by 1% and 2% ciprofloxacin-containing filaments (18.00 ± 6.12 mm and 19.40 ± 2.19 mm, respectively) and discs (16.80 ± 4.92 mm and 19.60 ± 5.13 mm, respectively) were significantly smaller than those of the PLA pellets ($p < 0.0001$). This difference could be explained by the fact that ciprofloxacin powder covered a significant part of the surface of the pellets and therefore showed a better antibacterial effect on *E. coli*. However, since some of the antibiotic powder became embedded in the inner parts of the materials during the filament extrusion and 3D printing processes, this might have limited the antibacterial effect. The zone diameters of ciprofloxacin-containing filaments and discs were not statistically different ($p > 0.05$). This finding suggests that following the extrusion of filaments, antibacterial activity of ciprofloxacin was not significantly affected by further exposure to heat and process in the 3D printing stage (Table 2 and Figure 5).

The results obtained in the diffusion tests are comparable to the findings of Weisman *et al*. who reported that 2.5% gentamicin-coated PLA pellets and filaments produced inhibition zones that averaged 29.03 ± 2.78 mm and 23.12 ± 0.79 mm, respectively. The discs containing gentamicin at 1% and 2.5% concentrations generated inhibition zones averaging 12.9 ± 2.56 mm and 21.35 ± 1.0 mm, respectively [6]. Our results are consistent with the findings of Weisman *et al*. who observed that filaments and discs containing 2.5% gentamicin generated similar inhibition zones, which were smaller than that of PLA pellets [6].

Our study was limited because we could not perform morphological (scanning electron microscopy), spectrophotometric and drug release studies to further examine our ciprofloxacin-impregnated filaments and discs. Therefore, antibiotic particles, which were distributed on the surface or embedded within the filaments and discs, could not be evaluated with direct visualization, and their amount could not be quantified.

Conclusions

In this study, ciprofloxacin retained its antibacterial activity after exposure to high temperatures during filament extrusion and 3D printing processes. Diffusion tests indicated that PLA pellets, filaments and 3D discs that contained 1% or 2% ciprofloxacin had antibacterial effects and produced inhibition zones in the culture plates inoculated with *E. coli*. Increasing ciprofloxacin concentration did not significantly affect the antibacterial activity. In addition, compared to the inhibition zone diameters of antibiotic-containing filaments, additional heat during the printing stage did not reduce the antibacterial activity of ciprofloxacin-impregnated discs. In combination with previously published data, these findings suggest that ciprofloxacin can be one of the potential antibiotics to be used for 3D printing of PLA-based antibiotic-impregnated materials. This approach may be used for designing and printing 3D implants or meshes tailored for patients with contaminated surgical sites. Therefore, we believe that our study can provide a basis for future studies to evaluate the efficiency of ciprofloxacin-impregnated PLA materials using in vivo models.

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