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Preliminary mechanical characterization of poly(D,L-lactic acid),
polydioxanone, and type I collagen electrospun scaffolds

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Abstract

Impaired wound healing continues to be a significant clinical challenge, with contributing conditions such as diabetes, cardiovascular disease, and obesity increasing in prevalence. Electrospinning, a technique for fabricating fibrous biomaterials, shows promise for improving wound healing as well as serving as a platform for drug-delivery applications. Poly(D,L-lactic acid) (PDLLA) is a polymer extensively researched as microspheres in injectable dermal fillers, but there is limited research on PDLLA in other configurations, such as electrospinning. This study aimed to quantify the tensile mechanical properties of electrospun scaffolds fabricated with varying concentrations of PDLLA, polydioxanone, and type I collagen, evaluating the ultimate tensile strength (UTS) and Young's modulus relative to experimental values for native skin tissue. Results demonstrated that while the UTS of each sample did not reach the reference values for skin, the blend consisting of PDLLA, polydioxanone, and collagen exhibited a Young's modulus closest to the reference values. The addition of PDLLA to electrospun scaffolds demonstrates an increase in elasticity while decreasing UTS, giving further insight into potential future applications for this polymer. With PDLLA's applications in drug delivery, the incorporation of PDLLA in electrospun scaffolds increases possible clinical uses for improving outcomes in impaired wound healing cases.

Introduction

Wound healing is an essential process that occurs in response to tissue injury, involving complex interactions between multiple bodily systems. Injuries to bodily tissues occur regularly so the processes within healing these injuries must remain functional, as disruptions can lead to infection or further injury [1]. Impaired wound healing is becoming increasingly common, with contributing factors not limited to obesity, diabetes, stress, and cardiovascular disease [2]. Understanding the mechanisms of wound healing, as well as how disease disrupts essential cellular functions, ultimately leads to innovative approaches to addressing clinical challenges arising from tissue injury.

One solution for healing wounds uses a scaffold that first anchors cells, thus allowing them to reconstruct a native body extracellular matrix, all without stimulating a response from the immune system [3]. One biomaterial fabrication technique, electrospinning, was selected because its fiber size and orientation mimic the structure of the extracellular matrix [3], one of the primary locations where wound healing occurs. This technique involves placing a syringe of polymer solution on a pump and charging the solution via a voltage source, so that the resulting solution forms a liquid jet out of the needle tip. The jet then creates polymer fibers as the solvent evaporates, and the fibers deposit on a collector to form a non-woven mat [4]. In addition to biocompatible polymer, an active pharmaceutical ingredient (API) may be incorporated into an electrospun scaffold to treat specific diseases or improve clinical outcomes. There are several methods to integrate pharmaceuticals, including but not limited to postspinning modification, blending the API with the electrospun solution, and coaxial electrospinning with a blended core and a polymer shell [5].

Poly(D,L-lactic acid), commonly referred to as PDLA, is a biodegradable polymer studied in dermatology as an injectable dermal filler. Specifically, PDLA promotes collagen synthesis and tissue regeneration, two ideal characteristics for a dermatological biomaterial. There are several well-researched applications for PDLA currently under study or marketed, ranging from treatments for facial wrinkles to cancer drug delivery. One preliminary study focused on the marketed formulation Juvelook (VAIM Inc., Republic of Korea) which uses injected PDLA in addition to non-cross-linked hyaluronic acid, and found that this combination increased skin elasticity, firmness, and hydration. Other studies have focused on specific skin concerns, such as treatments involving injected Juvelook to improve the appearance of stretch marks. Multiple studies with high patient satisfaction rates, in addition to limited adverse reactions, marks potential in a promising treatment for common skin concerns [6]. One study by Wang et al. indicates that loading the cancer drug rapamycin onto a PEO/PDLA nanofiber mesh shows promise as a targeted drug delivery system for glioma and other malignant cancers [7].

Since PDLLA and PDLLA blends demonstrate potential across different cell types, including the skin as well as the supportive glial cells affected by glioma [8], there is a broad array of possible clinical applications across medical specialties. Research on PDLLA has primarily focused on spherical microparticles, and studies have yet to thoroughly examine its properties in other configurations, such as nanofibers formed by electrospinning. Biocompatibility, along with slow and controlled degradation, solidifies PDLLA as an excellent candidate in tissue engineering and regenerative medicine [6].

Polydioxanone (PDO) is a polymer extensively studied for its biodegradability and compatibility within the human immune system, especially within the context of PDO as a biodegradable monofilament suture. Despite commercial use limiting PDO usage to sutures, this polymer exhibits beneficial mechanical properties as an electrospun scaffold. Shape memory properties displayed by PDO sutures are observed in electrospun mats as well, indicating possible future use in tissue engineering applications [9]. Type I collagen is a common structural protein within the body, primarily found in interstitial extracellular matrix. Due to its role in structural tissue support, collagen exhibits rigidity, resistance to stretching [10], and biocompatibility, making it a model for ideal electrospun material characteristics that mimic the extracellular matrix. These mechanical characteristics are due to collagen's fibril-forming structure, where fibril diameters and organized arrangements vary across bodily tissues depending on the system's need for structural support [11]. PDO and collagen have established prominence in tissue engineering due to their ideal wound healing characteristics, thus a PDO and type I collagen blend serves as the control group for this study.

Evaluating biomaterials for medical applications involves a wide range of tests, including mechanical testing. Assessing the mechanical properties of a biomaterial suggests potential medical applications, especially when compared to materials already found within the body. In general, mechanical evaluation for electrospun materials occurs under tension, where the values for material stress and strain provide the material's ultimate tensile strength, percent elongation, and Young's modulus. Ultimate tensile strength is the maximum amount of force that a material can withstand before breaking, and percent elongation is the amount of material deformation in relation to its original size. Young's modulus is a calculation that shows the material's stiffness, where a high Young's modulus suggests significant material deformation and thus high elasticity. These three significant pieces of information provide a solid foundation for understanding a specific biomaterial and its medical relevance when comparing to native tissues. This study aims to quantify the mechanical properties of PDLLA and PDLLA-containing electrospun blends, comparing them to a PDO and collagen control group.

Materials & Methods

Solutions consisting of collagen (type I collagen isolated from rat tails), polydioxanone (PDO, DIOXOMAXX®100, inherent viscosity 1.7 dL/g, Bezwada Biomedical, Hillsborough, NJ, USA), and poly(D, L-lactic acid) (PDLLA, inherent viscosity 1.62 dL/g, Bezwada Biomedical, Hillsborough, NJ, USA) in various concentrations were added to 4 mL of 1,1,1,3,3,3-hexafluoro-2-propanol (HFP, Thermo Fisher Scientific Inc., Waltham, MA, USA) and allowed to dissolve overnight. Four solutions were created, with specifications listed in Table 1.

PDLLA	400 mg PDLLA, 4 mL HFP
PDLLA, collagen blend	400 mg PDLLA, 40 mg collagen, 4 mL HFP
PDO, collagen blend	400 mg PDO, 40 mg collagen, 4 mL HFP
PDO, PDLLA, collagen blend	200 mg PDO, 200 mg PDLLA, 40 mg collagen, 4 mL HFP

Table 1.

Initial solutions with specific quantities involving PDLLA, PDO, collagen, and HFP.

Once dissolved, solutions were transferred to 5 mL Luer-Lok™ syringes (Becton, Dickson and Company, Franklin Lakes, NJ, USA) equipped with an 18-gauge, 2-inch blunt needle (McMaster-Carr, Elmhurst, IL, USA). The syringe was placed onto a KDS Legacy 100 Syringe Pump (KD Scientific, Holliston, MA, USA) set at varying flow rates from 1.2 mL/h to 2.0 mL/h, as well as varying voltages from 20 kV to 28 kV, adjusting to ensure proper fiber deposition. One sample of each solution composition was collected via the traditional electrospinning technique. Five samples of a 20 mm gauge length dog-bone shape were cut from each sample for tensile testing.

Samples were fixed on a uniaxial testing frame (Model Q CONTROLLER, Test Resources, Shakopee, MN, USA) and evaluated under tensile stress. Grips were separated at 10mm/min until failure, and data were recorded in Newtons (N) at 50 samples per second. Material stress was recorded alongside the grips' displacement. The ultimate tensile strength (UTS) in megapascals (MPa) was calculated by the frame controller using the input initial cross-sectional area. Percent elongation and Young's modulus were then computed using a MATLAB script. Data is reported as both raw values and mean ± standard deviation.

The raw values were then analyzed statistically using GraphPad Prism. Calculations produced from the MATLAB script were analyzed for normality before any further statistical testing. Normality testing demonstrated the normal distribution of the UTS and Young’s modulus data, indicating the use of a BrownForsythe and Welch ANOVA. However, testing showed that percentage elongation data groups were not normally distributed, so a Kruskal-Wallis test was used instead. Groups were compared for statistical significance against the PDO and collagen control.

Results

The raw mechanical testing data in megapascals (MPa) for ultimate tensile strength (UTS) is shown in Table 2. The mean values in decreasing order are the PDO/collagen blend with 6.51 ± 0.55 MPa, the PDLA/PDO/collagen blend with 6.17 ± 0.31 MPa, the PDLA/collagen blend with 5.48 ± 0.82 MPa, and lastly the PDLA solution with 4.11 ± 0.13 MPa. The PDLA solution was the only group significantly weaker than the control with a p-value less than 0.01. The ultimate tensile strengths of the four groups in a box-and-whisker plot format are shown in Figure 1. Statistical analysis was performed using a Brown- Forsythe and Welch ANOVA.

PDO/Collagen	PDLA	PDLA/Collagen	PDLA/PDO/Collagen
6.72	4.09	6.51	5.98
5.68	4.21	4.23	6.61
7.01	3.89	5.41	6.17
6.91	4.21	5.53	6.30
6.22	4.15	5.73	5.81

Table 2.
Ultimate tensile strength raw data (MPa).

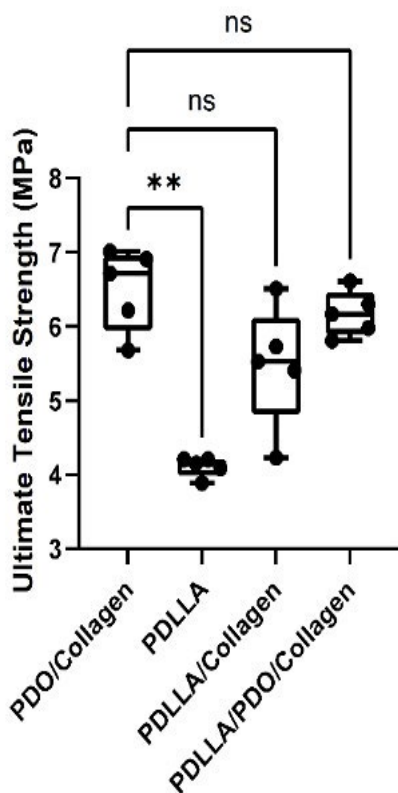


Figure 1.

*Box-and-whisker plot of ultimate tensile strength (MPa) for PDO/collagen, PDL-
LA, PDLLA/collagen, and PDO/PDLLA/collagen electrospun scaffolds. Asterisks
indicate statistically significant differences (** denotes $p < 0.01$).*

Mechanical testing data for elongation are displayed in Table 3 as per-
centages. The mean values in decreasing order are the PDLLA solution at $820.7 \pm 36.44\%$, the PDO/collagen blend at $202.28 \pm 33.27\%$, the PDLLA/collagen blend
at $177.17 \pm 38.39\%$, and the PDLLA/PDO/collagen blend at $140.20 \pm 13.73\%$.
None of the tested groups were significantly different than the control. The percent-
age elongation of each group is shown in a box-and-whisker format in Figure 2.

PDO/Collagen	PDLLA	PDLLA/Collagen	PDLLA/PDO/Collagen
242.10	808.77	245.03	136.00
158.12	800.77	154.65	150.65
197.28	885.55	158.82	152.90
186.67	800.77	157.25	142.72
227.25	807.68	170.10	118.75

Table 3.
Percent elongation at break (%)

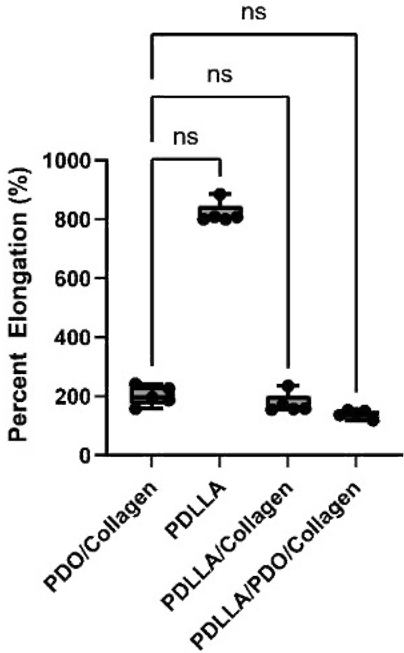


Figure 2.

Box-and-whisker plot of elongation as a percentage for PDO/collagen, PDLLA, PDLLA/collagen, and PDO/PDLLA/collagen electrospun scaffolds.

Young’s modulus in megapascals for each group are shown in Table 4, and a box-and-whisker plot is shown in Figure 3. The mean values in decreasing order are the PDLLA/PDO/collagen blend at 77.39 ± 11.72 MPa, the PDLLA

solution at 49.13 ± 11.97 MPa, the PDLLA/collagen blend at 40.98 ± 27.97 MPa, and the PDO/collagen blend at 30.97 ± 8.26 MPa.

PDO/Collagen	PDLLA	PDLLA/Collagen	PDLLA/PDO/Collagen
34.05	64.16	5.28	68.43
21.50	42.50	23.88	83.45
40.18	32.67	76.78	79.16
23.05	53.51	57.76	63.32
36.08	52.81	41.19	92.59

Table 4.
Young’s modulus data (MPa).

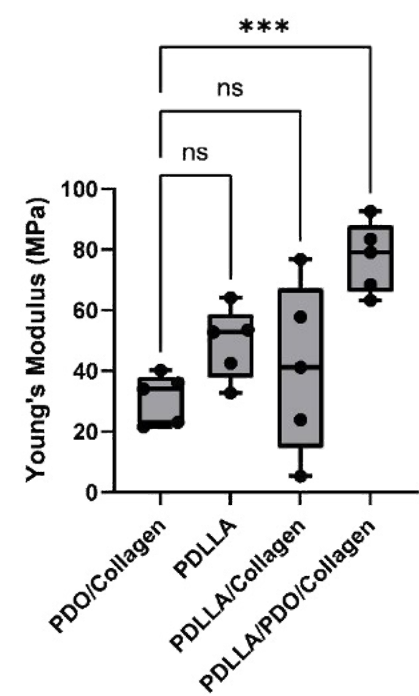


Figure 3.
*Box-and-whisker plot of Young’s modulus (MPa) for PDO/collagen, PDLLA, PDL-
LA/collagen, and PDO/PDLLA/collagen scaffolds. Asterisks indicate statistically
significant differences (***) denotes $p < 0.001$).*

Discussion

Grafts consisting solely of PDLLA scaffolds exhibited high elongation at break but low ultimate tensile strength. This suggests that PDLLA scaffolds can be applied to systems where tissues do not experience much mechanical load but still need the ability to stretch with movement. With the addition of type I collagen to PDLLA, tensile strength increased while elongation at break decreased. The blend consisting of PDLLA, collagen, and PDO resulted in the highest elasticity shown by the Young's modulus as well as a UTS similar to the control PDO and collagen blend, but it exhibited the least amount of elongation. This study suggests an inverse relationship between elasticity and tensile strength when collagen and PDO are added to PDLLA.

The Young's modulus of the PDO, PDLLA, and collagen blend exhibits the most similarity to native skin tissue reported by Annaidh et al. [12]. The blend in this study exhibited a Young's modulus of 77.39 ± 11.72 MPa, compared to the average 83.3 ± 34.9 MPa reported by Annaidh et al. However, the PDO, PDLLA, and collagen blend exhibited a UTS of 6.17 ± 0.31 MPa, contrasting the reference UTS of native skin tissue at 21.6 ± 8.4 MPa. Because of the significant difference in Young's modulus between the PDO/collagen and the PDLLA/PDO/collagen samples, this study suggests that the addition of PDLLA increases elasticity in electrospun scaffolds.

PDLLA-containing scaffolds exhibit distinct mechanical characteristics relative to other electrospun polymer nanofibers, such as polycaprolactone (PCL) and polyglycolic acid (PGA). Relative to the results obtained by Aghdam et al., the average UTS of the PDLLA/collagen and PDLLA/PDO/collagen blends show greatest similarity to the PCL/PGA blend at a 50/50 weight ratio [13]. The PDLLA-containing blends exhibited greater elongation and Young's modulus than the blends studied containing PCL and/or PGA. Incorporating PDLLA into blends containing PCL and PGA may increase elasticity if desired for specific clinical use.

One limitation in this study is the variability in conditions across electrospun samples. Differences in ambient conditions, specifically humidity, necessitated adjustments to voltage and flow rate that may account for variability across samples. Future studies will benefit from the uniformity of fabrication parameters. Further research is needed in other aspects of these polymers to understand their full potential within tissue engineering. Future work to analyze pore sizes and nanofiber structures may clarify the reasoning behind these mechanical observations as well as inform the direction of biocompatibility testing.

Wound healing assays or studies on fibroblast infiltration and migration would be beneficial, as well as various assays that quantify the immune response to these specific biomaterial blend ratios, adding more information for optimal cell

compatibility of a PDLLA electrospun material. Additionally, electrospun materials incorporating PDLLA could serve as a route for drug-delivery applications. Previous studies have analyzed electrospun polymers incorporating drugs, including-steroidal anti-inflammatory drugs (NSAIDs) and antibiotics [3]. Given mechanical differences between PDLLA and previously investigated polymers, PDLLA warrants further investigation to determine its potential in drug-delivery systems.

Conclusion

This study aimed to mechanically characterize four polymer solutions as traditionally electrospun scaffolds, with results to suggest future studies based on similarities to native tissues in the human body. The different polymer blends exhibited distinct mechanical characteristics under tensile stress. Seen with the addition of type I collagen to blends of PDLLA and PDO, these findings suggest an inverse relationship between elasticity and material strength. Ratios in these blends present trade-offs, so the mechanical properties required must be considered when selecting a polymer or blend for biomedical applications.

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