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In vitro study and characterization of cotton fabric PLA composite as a slow antibiotic delivery device for biomedical applications

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ABSTRACT

Wound treatment remains a challenge to many clinicians because of the complexities of the wound healing process. The choice of dressing depends on a number of factors such as wound type, location, and injury extension, as well as the patient's health status. All of these factors increase the complexity and difficulty of utilizing a single type of dressing. The focus of this study was centered on developing a woven cotton fabric polylactic acid (PLA) composite as a low drug delivery device for biomedical applications. A hand weaving method was employed in developing the fabric to control its porosity. Fabrics with three different pore sizes 0.5 mm, 1.0 mm, and 1.5 mm were developed with a natural cotton yarn of 36 Tex and the resulting fabrics were used for composite development. Three different PLA concentrations 0.01 g/mL, 0.03 g/mL, and 0.06 g/mL were used to study the effects of the PLA/fabric ratio on the mechanical properties. The antibiotic amoxicillin was used in the study. This drug release study was monitored by UV-Vis spectrophotometry, while mechanical testing was performed with the Instron 5566 universal materials testing system. The results suggested that drug-loading capacity increases with decreasing fabric porosity. The release profiles from these devices followed a two-stage pattern, and the release mechanism appears to be a mixed transport system. This includes diffusion and possibly super case II kinetics, as well as a release due to damage to the composite surface through dissolution. The amount of released concentration exceeded the minimum inhibitory concentration of amoxicillin against *Staphylococcus aureus*. Degradation of the fabric composites is suggested as influencing the drug release rate. The water absorption ability of composites decreases with increasing PLA concentrations. The mechanical properties of composites were consistent with the fabric's density and weight. To design the ideal wound dressing materials, consideration of all these aforementioned properties are required in order to incorporate the desired functions to support tissue regeneration and healing while limiting bacterial infections. The findings from this research suggest that the developed devices could be used for wound dressing applications on sites where a water-resistant dressing is required, thus aiding in the prevention of bacterial contamination of the primary dressing.

1. Introduction

Skin serves primarily as the essential barrier protecting organisms from their environment [1,2] and plays a role in thermoregulation. Skin is composed of three layers: epidermis, dermis, and hypodermis. The dermis layer provides support and nutrition to the epidermis. A wounded epidermis can stimulate self-regeneration and healing; however, this process is slow and can be affected by age and health status. Several strategies are available for the treatment of skin damage such as autografts, allografts, wound dressing, and tissue engineering substitutes [1]. In particular, a deeper dermal wound of more than 4 cm in diameter requires a graft for treatment. It is globally estimated that burns cause 265,000 deaths every year. In India, over 1,000,000 people are moderately or severely burnt every year. In 2016, over 486,000 burn injuries occurred and received medical treatment in the United States, with approximately 40,000 requiring hospitalization. Direct costs for the care of children with burns in the United States exceeded US$211 million. In Norway, costs for hospital burns management in 2007 reportedly exceeded €10.5 million [3]. Wound healing normally undergoes three phases: inflammatory, proliferation, and maturation. During these phases, damaged tissues are restored through coordinated signaling that constitutes the cutaneous healing response.

Despite the considerable progress in recent years, wound healing remains a challenge for many clinicians and researchers regardless of their professional discipline or experience in the development of novel and efficient wound dressings. Dressing choice should be based on the dressing's ability to provide or maintain a moist environment, enhance epidermal migration, promote angiogenesis and connective tissue

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synthesis, as well as allow gas exchanges between the wounded tissue and the environment. It must also maintain appropriate tissue temperature to improve the blood flow to the wound bed and enhance epidermal migration. Furthermore, it must provide protection against bacterial infection and debridement action to enhance leukocytes' migration. The dressing should be non-adherent to the wound for ease of removal after healing; it must also be sterile, non-toxic, and non-allergic [4]. However, it is difficult to find dressing materials that fulfill all these requirements, and the choice of the correct dressing depends on the wound type and stage, injury extension, patient condition, and involved tissues [5].

Traditional wound dressing products include gauze, honey pastes, plant fibers, animal fats, plasters, bandages (natural or synthetic), cotton, and wool used as primary or secondary dressings for protecting a wound from environmental and bacterial contamination [4,6,7]. However, some of these dressings do not meet the requirements for rapidly healing wounds, due to wound adherence causing ischemia/necrosis and frequent changes [7]. Gauze dressings made of woven and nonwoven fibers of cotton, rayon, and polyester afford some protection against bacterial infections. However, these dressings require frequent changing to protect against the maceration of healthy tissues.

Animal model studies have shown that when a wound is kept in a moist condition, as would have resulted from the application of an occlusive film dressing, epithelialization of the wound surface occurred at a much faster rate than in a dry condition, which was then regarded as the desirable condition. Studies on human wounds confirmed that the wound healing rate increased when the wound was kept in a moist condition [8].

Due to increasing environmental awareness, biocomposites are becoming the most important material. The development of eco-friendly products made from natural resources is increasing worldwide [9]. Natural fibers such as flax, cotton, hemp, silk etc. have been used to reinforce thermoplastics due to their advantages, such as low cost, low weight, acceptable specific strength, good thermal insulation properties, biodegradability, and, most important, renewability. As such, eco-friendly composites may be used for many applications including biomedical wound dressings [10,11]. It is suggested that natural fibers suitable for wound dressing include cotton, silk, and linen [12].

There is minimal literature [13] regarding the use of cotton woven fabrics, or PLA composites, as drug delivery devices for wound dressing applications. Our study aimed at providing a novel approach towards the preparation of cost-effective slow antibiotic delivery devices as wound dressing materials. In addition, these materials have some wide range applications for cellulose polymer composites materials for future wound care applications.

2. Materials and methods

2.1. Materials

Polylactic acid (PLA) 3052D (specific gravity = 1.24, Tg = 55–60 °C, MP = 200 °C) with Mw = 75,000 (g/mol) was obtained from Nature Works LLC Australia. Chloroform with a ≥99% assay, amoxicillin (potency: ≥90 μg per mg), and sodium hypochlorite (NaOCl) were obtained from Sigma Aldrich Kenya. Chemicals for PBS were purchased from a local supplier. Cotton yarns were kindly donated by Urafiki Textile Company, Tanzania.

2.2. Methods

2.2.1. Preparation of cotton woven fabric

Fabrics with different pore size (0.5, 1.0, and 1.5 mm) were handmade using a cotton yarn of count 38 Tex on a 30 cm by 30 cm dimensional template with equally spaced warp and weft. The reason for hand-making was to control the pore size of the fabric, which affects the drug loading and dissolution. During the weaving process, yarns were inserted in the longitudinal direction that acted as the warp yarns were followed by the yarns in the horizontal direction and served as the weft yarns. After fabrication, the pore sizes of the fabrics were corrected by hand. Three samples from each pore size were made and stored in desiccators for further use.

2.2.2. Antibiotic loading into the fabric

Hand-woven cotton fabrics were cut to 6 cm × 5 cm pieces and served as drug delivery devices. They were gently washed in 2% NaOCl in order to remove any residual oils and then thoroughly rinsed with distilled water. The cleaned specimens were dried in an oven at 50 °C for 48 h before use. Drug loading was done by making three different amoxicillin concentrations (0.10, 0.08, and 0.06 mg/mL) equivalent to 10%, 20%, and 30% w/w, respectively, in deionized water, and then the samples were totally immersed in the drug solutions for 10 min. After 10 min, the samples were put on Petri dish and allowed to dry under room temperature in a fume hood for 72 h. Weights of specimens were recorded before and after loading the drug.

2.2.3. Preparation of woven fabric PLA composite

The woven cotton fabric PLA composites for this drug dissolution study were prepared using a solvent casting technique described previously [14,15]. Briefly, 0.01 g/mL, 0.03 g/mL and 0.06 g/mL of PLA solution in chloroform were prepared by dissolving an appropriate amount of PLA in chloroform under magnetic stirring on a hot plate and gently heating the mixture at 50° C until the PLA dissolved completely. Then drug-loaded samples were placed in a Petri dish, and then the solution of PLA was poured over until all samples were submerged completely. The process of composite development was carefully done to ensure a uniform distribution of PLA in the woven cotton fabric. Then solvent evaporation took place under small vacuum for 72 h after which the samples were stored in a desiccator for further studies.

Composites for mechanical testing, water absorption, and degradation studies were prepared by casting 150 mL of PLA solution of 0.01 g/mL, 0.03 g/mL, and 0.06 g/mL concentration on a 30 cm × 20 cm woven cotton fabric in a plate template covered by aluminum foil. The experiments were performed using cotton fabrics with different pore sizes, as mentioned above. The weights of the samples were recorded before and after composite development. Samples for mechanical testing were cut into 10 cm × 5 cm, a total of five samples were prepared for each pore size and PLA concentration. Degradation and water absorption studies were conducted on 4 cm × 4 cm composite specimens.

2.2.4. Drug dissolution and quantification study

A drug dissolution study of woven cotton fabric and PLA composites was conducted under SINK conditions in phosphate buffered saline (PBS) (0.1 M, pH 7.4) at 37 ± 0.1 °C in a temperature-controlled oil bath shaker running at constant speed of 100 rpm. The experiment was designed so that each sampling time had its own independent samples running simultaneously under the same conditions and the experiments were each terminated after sampling. This was to avoid kinetic changes if some volume was to be taken and replaced with the fresh PBS solution. All drug concentrations were determined by a Milton Roy Spectronic 21D UV-Visible Spectrophotometer (Milton Roy Company, USA) at the maximum absorbance of amoxicillin, λ_{max} = 496 nm using procedures described in Ref. [14]. The absorbance, which corresponds to the amoxicillin concentration, was measured from the dissolution samples and used to calculate the actual drug concentration using a calibration curve prepared for each set of measurements.

2.2.4.1. Drug release kinetics. Drug dissolution mechanisms from the composites were studied by fitting the dissolution results to various mathematical models selected from literature based on the known properties of the composites' constituents. The model characterized diffusion, dissolution or erosion, and mix or dissolution-diffusion

processes.

2.2.5. Degradation study

A degradation study of composites was conducted in a PBS solution (0.1 M, pH 7.4) at 37 ± 0.1 °C for 14 days. Five specimens were used for each PLA concentration and their weights before the study were recorded. After this time, samples were taken from the solution, rinsed with distilled water, and then dried in an oven at 50 °C with constant monitoring of their weight. Weight loss was recorded and considered a measure of the materials' degradation.

2.2.6. Water absorption study

Water absorption testing was conducted by drying composite specimens in an oven at 50 °C for 72 h, then cooled in a desiccator. Cooled samples were immediately weighed and immersed in water at 23 °C for 24 h. The composite specimens were removed, patted with lint-free cloth, and weighed. Water absorption was expressed as an increase in weight.

2.2.7. Mechanical testing

The mechanical testing of composite samples was performed by means of tensile tests, according to Tanzania Bureau of Standards (TBS) *Tanzania Standards (TZS) 22:1979* (1st Ed) titled, "Textile Woven-Fabric Determination of Breaking Load and Extension." Tests were carried out in a universal tensile testing machine (Instron 5566, Series IX Automated Materials Testing System 8.25.00) with a crosshead speed of 100 mm/min and the load cell of 10 kN. Deformation was followed with Blue Hill 3 software version 3.41. Five specimens of each composite with a gauge length of 100 mm and a width of 50 mm were tested. Also, the untreated or neat woven cotton fabric specimens were tested for comparison.

3. Results and discussions

Hand-woven cotton fabrics were characterized in terms of their physical properties using the ASTM D5446–08(2013) standards, as shown in Table 1. Notably the fabrics have same number of warp and weft so that they have the same fabric density in both directions. The fabric cover factor indicates how well the area underneath the fabric is covered by the fabric and the yarns. The yarn crimp was used to describe the degree of waviness of yarn in a fabric. Fabric weight is the measure of substance contained in a fabric and reflects the mechanical properties such as strength of the fabric. The results showed that these fabrics' physical properties are consistent with the pore sizes.

Fig. 1 shows the two-stage, slow-release profiles of amoxicillin from loaded composites. The effect of the amount of drug loaded indicates that the highest drug fraction was released from the highest loaded composites (Fig. 1a). Cotton pore sizes affect both the amounts loaded and their release from the composites. These results suggest that the composites with a pore size of 0.5 mm had the highest drug amount released at all times. The results also suggest that the drug released from three cotton fabric composites with different pore sizes followed a similar pattern. At a low drug concentration, most of the loaded drug was apparently coated with PLA and this affected the initial release of the drugs.

The release of antibiotics from the cotton fabric composites followed two stages: a rapid short release of the drugs and a stable "plateau" profile. However, the clinically active agent released from the drug carrier followed a similar patterns but with three stages [16]. The first stage was the bursting that released the drugs on the surface of the fabrics that were not coated well with PLA. At the beginning, the buffer solution penetrated into the uncoated fabric and hydrated the fabric and the matrix. This process occurred very quickly, especially for bulk eroding matrices. As the fabric and matrix hydrated, the drug loaded on the surface of the fabrics and adjacent to the matrix diffused into a buffer solution in the phase that is usually known as the "initial burst." Its magnitude depends entirely on the amount of the drug adjacent to the matrix and the amount of the uncoated drug on the surface of the cotton fabric. This could be explained as the direct dissolution of the drug in a PBS solution. This stage took place during the first day of this drug release study for all devices and all concentrations.

After the initial bursting, the release profiles progressed into the second stage of drug release. In this stage, the polymer was hydrated by PBS solution and this began the degradation of its backbone chains. This phenomenon lead to the formation of more pores on the polymer surface to facilitate the drug diffusion from the cotton fabric. The drugs released from the composite were mainly by a diffusion mechanism and polymer degradation sped up the process. On the other hand, the control of the release rate of the degradable polymer can be tailored for different rates by manipulating the polymer's molecular weight. The heterogeneous degradation of the polymer matrix is believed to start in an amorphous region of the polymer matrix that leaves behind pores and creates a secondary surface porosity that is favorable for fluid transport phenomena and provides a further pathway for dissociation inside the composite.

Fig. 1c shows the smallest releasing of drugs from composites with different pore sizes, which suggests that the drug concentration was relatively small. The required number of drugs to be loaded into the delivery devices depends on the loading capacity and the combination of degradation rate and minimum inhibition concentration (MIC). The MIC of the antibiotic (amoxicillin) used in this study ranged above 16 μg/mL against *Staphylococcus aureus* [17,18]. The statistical analysis indicates that, at all release times, there is a significant difference in drugs released for fabric composites with different pore sizes.

Fig. 2 shows the release profiles of neat hand-woven cotton fabrics with different pore sizes. These results suggest that the release from a neat fabric follows two stages: burst effect and retarded drug release. The release rate from the neat fabrics exceeded the rate observed for the fabric composites. The effects of PLA in the composites regarding drug retardation or control release are significant. With neat fabrics, the fractional drug release ranged from 0.4 to 0.7, while with PLA composites the release rate ranged from 0.05 to 0.60. This discrepancy was caused by different factors, such as fabric pore sizes, amount of drug loaded, and the presence of PLA.

Fig. 3 shows the water absorption results of woven cotton fabric PLA composites with different PLA concentrations. The fabric composite reduced the absorbability of water as the PLA concentration increased. The water absorption property is also affected by fabric pore sizes. The smaller the pore size, the larger the amount of water absorbed. This is consistent with fabric weight or fabric density as shown in Table 1.

The effect of PLA concentration is very significant on the water absorption properties of fabric composites. Composites with a 0.5 mm

Table 1
Properties of the fabric samples prepared by the hand weaving method.

Fabric samples	Fabric thickness (mm)	Warp/weft spacing (mm)	Fabric density (1/cm)	Warp cover factor	Weft cover factor	Fabric cover factor	Fabric crimp	Fabric weight (g/m^2)
0.5 mm pore size	0.438	0.5	20.0	0.44	0.44	0.69	0.03	156.6
1.0 mm pore size	0.432	1.0	10.0	0.22	0.22	0.39	0.05	79.8
1.5 mm pore size	0.425	1.5	6.7	0.15	0.15	0.28	0.07	54.5

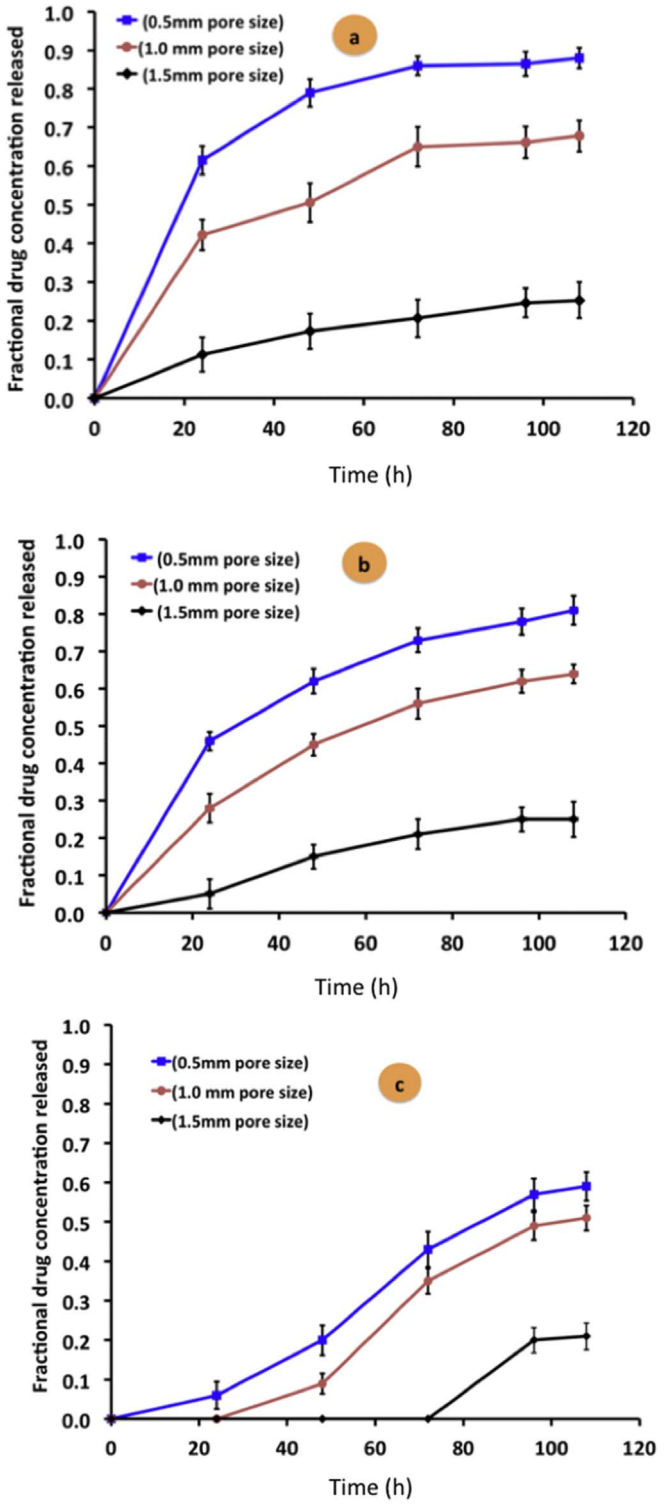


Fig. 1. Amoxicillin release a) composites loaded with 0.1 g/mL, b) composites load 0.08 g/mL, and c) composites loaded with 0.06 g/mL. Error bars are mean standard deviation (SD) of triplicate experimental data.

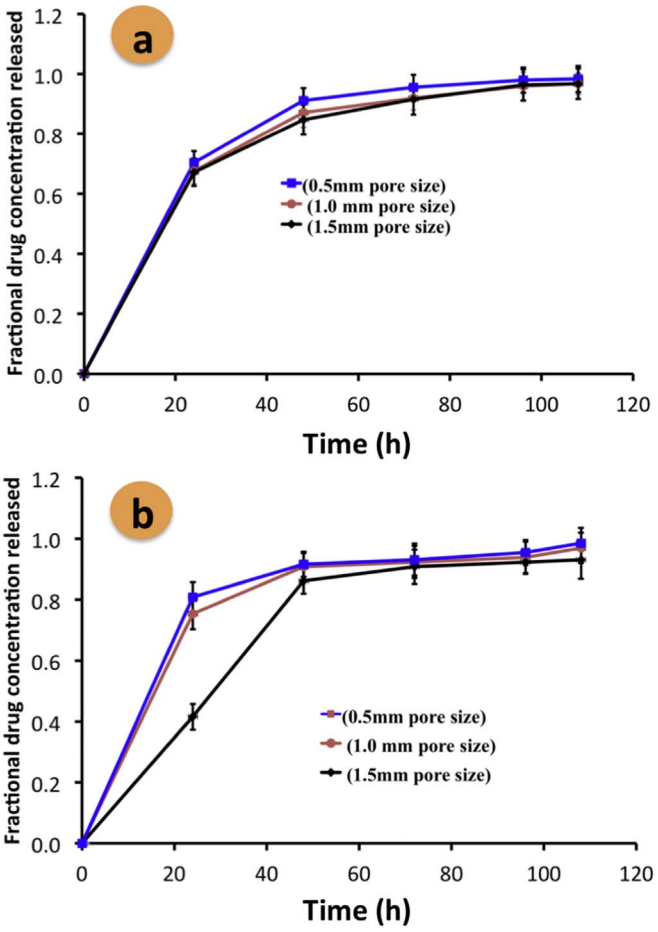


Fig. 2. Amoxicillin release profiles of a) cotton-woven, neat fabric loaded with 0.1 g/mL and b) cotton-woven, neat fabric loaded with 0.08 g/mL. Error bars are mean standard deviation (SD) of triplicate experimental data.

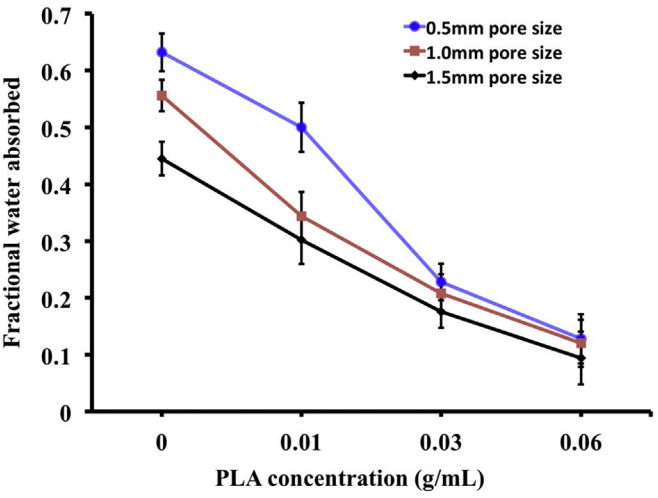


Fig. 3. Water absorption testing for the fabric composites with different PLA concentrations. Error bars are mean standard deviation (SD) of five experimental data.

pore size and a 0.01 g/mL PLA, for instance, lose 20% of their ability to absorb water and subsequently 64% and 81% for higher PLA concentrations of 0.03 g/mL and 0.06 g/mL, respectively. Water absorption properties influence polymer degradation and drug release, so it is important to consider this when designing biodegradable drug release systems.

A degradation study of 0.5-pore-size, woven-fabric PLA composites was conducted for two weeks and the weight loss was recorded. The results suggest that the PLA used in this study could significantly degrade in two weeks as shown in Fig. 4a. The fractional weight loss is consistent with the PLA concentrations used in the degradation study. The observed trend of a higher the PLA/fabric ratio the higher the fractional weight loss. The PLA with the specifications mentioned in Section 2 could be considered for both long- and short-term slow drug

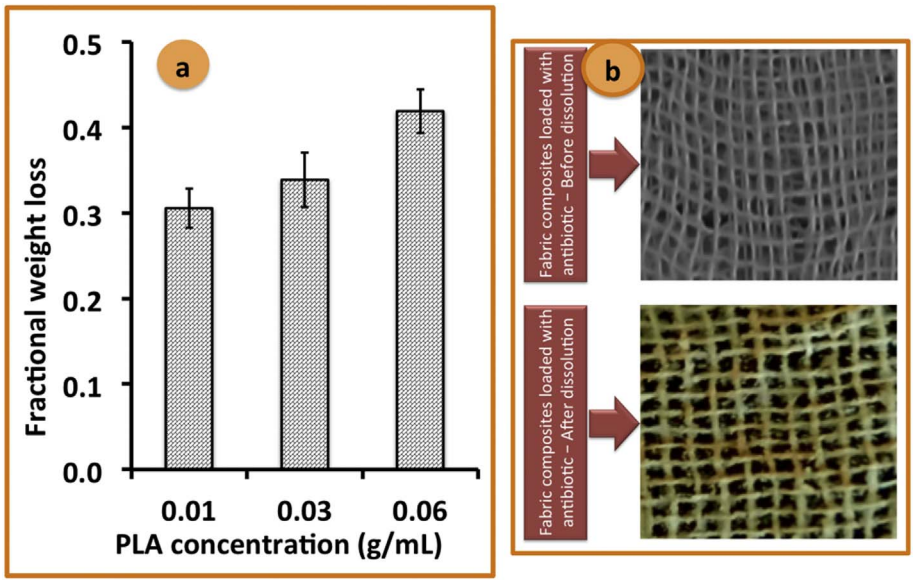


Fig. 4. a) Degradation study of the cotton fabric PLA composites. Error bars are the mean standard deviation (SD) of five experimental data. b) Photographs of fabric composites before and after drug dissolution that show the disruption of the PLA matrix due to their degradation.

release, which makes it appropriate for wound dressing applications. Its degradation rate could be tailored to suit a specific slow drug release. Fig. 4b shows significant disruption of the PLA matrix due to polymer degradation. The literature has indicated that the molecular weight is an essential parameter for controlling the spatial and temporal on-demand degradation and drug release from the delivery system [19]. The autocatalytic effect of the lactic acid and structural change of the matrix are other factors influencing PLA degradation and drug release kinetics. In cases of using a co-polymer, degradation could also be controlled by the co-polymer ratios based on their chemistry.

3.1. Release kinetics

The release of a clinically active agent from biodegradable systems can be a rather complex phenomenon governed by a number of mechanisms such as diffusion, dissolution, and erosion, and most often by a combination of these mechanisms. The release data were fitted to four selected models: Higuchi, Hixson-Crowell, Korsmeyer-Peppas, and Reciprocal powered time. The correlation coefficients (r^2) indicate that drug release kinetic of composites with 0.5 mm, 1.0 mm, and 1.5 mm fitted the power law model described by Korsmeyer-Peppas. Since it is difficult for a single model to describe all the mechanisms, we considered two borderline cases that correspond to distinct physical realities (when $n = 0.5$ and $n = 1$). The n coefficient obtained for composites with 0.5 mm and 1.0 mm pore sizes ($n \lessdot 0.5$) indicated that the release was mainly controlled by diffusion, while the value obtained for composite with 1.5 mm pore size ($n > 1$) suggested that the release mechanism was by mixed transport mechanisms, including diffusion and possibly super case II kinetics due to damage to the composite surface through dissolution (Figs. 1 and 4).

The mechanical tensile strength results of cotton-woven-fabric PLA composites are presented in Fig. 5. Different concentrations of PLA for different PLA/fabric ratios on different pore sized fabrics were used for comparison. The results show that the tensile strength of neat fabrics is consistent with fabric density and weight. Tensile strength decreased in order of increasing fabric pore sizes at any particular PLA concentration. The mechanical strength of composites seemed to increase with increasing PLA concentration, which signified a fair improvement of strength compared to neat cotton fabrics. This relatively strong affinity between matrix and cotton fabrics in which the surface chemistry of these materials supports that in Ref. [20]. In designing a drug release system, as long as the mechanical properties are not significantly compromised, a smaller PLA concentration could be used, depending on the applications. Conversely, in controlling the release, the drug or fabric has to be completely covered or coated with a PLA matrix.

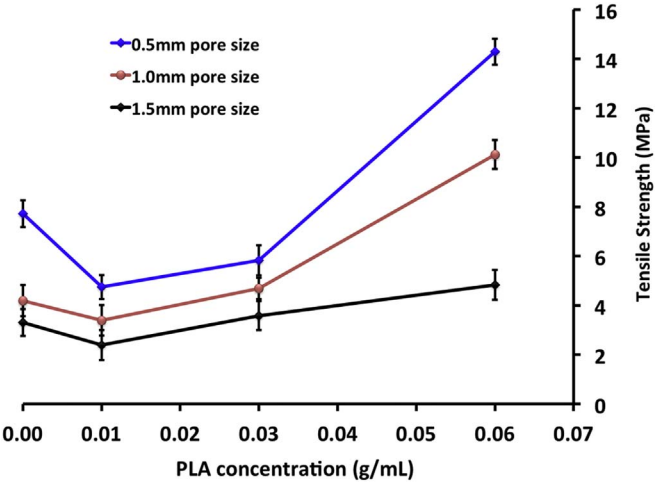


Fig. 5. Tensile testing on cotton fabric PLA composites. Error bars are mean standard deviation (SD) of five experimental data.

4. Conclusions

Woven-cotton-fabric PLA composite drug delivery devices were successful developed and *in vitro* studies were conducted to determine their release profiles, degradation behavior, and water absorption properties. Mechanical tensile strength characterizations of the composites were also studied.

The drug release profiles followed a two-stage release behavior that is common for degradable drug release systems. Statistical analysis showed significant differences of drug release from composites with different pore sizes. Differential pore sizes affect both the number of drugs loaded and released, as well as mechanical tensile strength and water absorption properties. Fractional weight loss due to degradation seemed to be consistent with the amount of PLA in the composites.

In contrast, degradation rates were observed to be similar for all composites. The strength of fabric composites increased with an increase in PLA content in the composites, which supports the effective reinforcement of PLA with cotton fabrics. These newly developed devices could be used for wound dressing applications at wound sites

where a water-resistant dressing is required to aid in the prevention of bacterial contamination as a primary dressing.

Conflict of interest

The authors declare no conflict of interest.

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