PCL^{Col}/PVA^{HA} coaxial electrospun nanofibers for controllable and sustained drug release

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Statement of Purpose: Failure of osseointegration (direct anchorage of an implant by bone formation at the bone-implant surface) and implant infection (such as that caused by methicillin resistant *Staphylococcus aureus,* MRSA) are the two main causes of implant failure and loosening. The aim of this study was to develop "bone-like" PCL^{Col}/PVA^{HA} core-sheath nanofibers (NFs) to promote osseointegration and inhibit MRSA colonization and subsequent infection by sustained delivery of Doxycycline (Doxy) and Dexamethasone (Dex) from coaxial NFs.

Methods: A Polycaprolacton (PCL) mixture (0.2 mg/mL) was prepared by dissolving PCL into chloroform through overnight homogenize. Additionally, 10mL of dimethylformamide (DMF) was added to the mixture and stirred for 3 hours until it was evenly homogenized. During the coaxial electrospinning a customized spinneret is employed to trap a secondary fluid layer (PVA, as a core fiber, was used as a drug reservoir for controllable drug release) within the core of the forming NFs. The sheath solution acts as a guide and surrounds the core material (**Fig. 1**). The electrospinning process settings were: Flow Rate (Q)=7.8µL/min, Voltage (V)= 19-20kV, and a needle tip to plate collector distance=10cm. A modified *S. aureus* growth inhibition assay was used to measure the bactericidal activity. For Doxy release, 40 mg of NFs (encapsulating ~1 mg Doxy) were soaked in 2 ml of Mueller–Hinton broth inoculated with *S. aureus* (1 $x10^2$ CFU) and cultured at 37°C. At each time point, the broth was removed and replaced with the same amount of broth. The optical density (OD) of collected broth was measured at 625 nm. All the tests were performed in triplicate and repeated two times. The concentrations of Dex (at OD of 242 nm) in the supernatant were determined using a UV–vis spectrophotometer

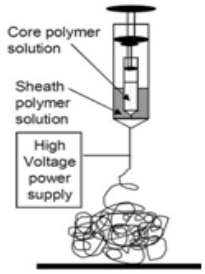

Fig 1. Spinneret for coaxial electrospinning

Results: As shown in **Fig. 2**, a distinguishable core-sheath structure of NFs was identified. The elemental composition analysis of NFs by EDAX showed the presence of Ca (from HA), C and O (from PVA, PCL), and N (from albumin and Col)A sharp boundary between the sheath and core fibers was observed by TEM (**Fig. 3**). The formation of distinguishable core-sheath NF structures results from the immiscibility of the two olymer solutions during electrospinning. We noticed that HA nanorods were properly embedded in the PVA core and some HA nanorods protruded through the PCL sheath layer. The core-sheath fiber ratio is ~1:5.

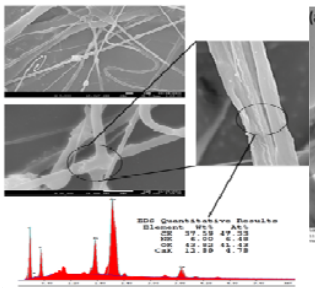

Fig 2. SEM micrograph of PCL^{Col}/PVA^{HA} coaxial NFs

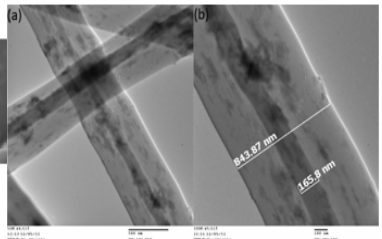

Fig 3. Representative TEM images of PCL^{Col}/PVA^{HA} coaxial NFs (a) Overlapping Fs showing distinguishable core-sheath :ructure, and (b)

Doxy embedded in NFs during coaxial electrospinning is stable and its bactericidal activity is proportional to the amount of Doxy loaded. Coaxial PCL/PVA core-sheath NF scaffolds represent a better device for a sustained and sufficient (> minimal inhibitory concentration) antibiotic release for at least 152 h. The Dex release profile is similar to the release of Doxy (**Fig. 4**). Similar to Doxy, blended PVA^{Dex}NFs showed a burst release within 10 h, and Dex was completely released within 48 h. Coaxial PCL/PVA^{Dex}NFs significantly extended Dex release for over 150 h.

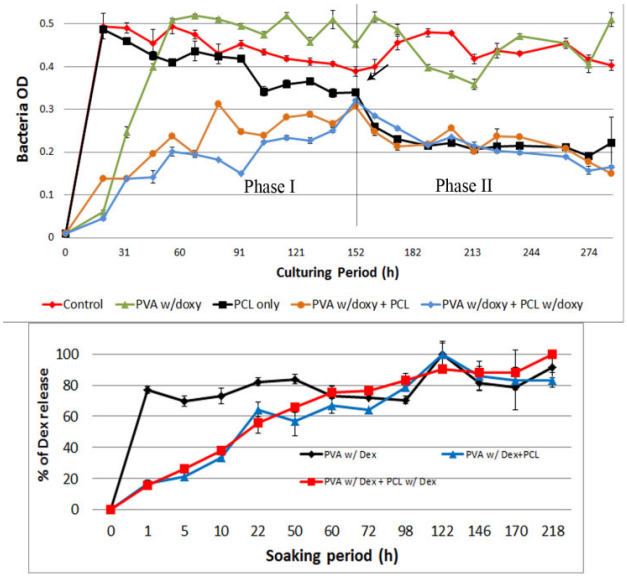

Fig 4. Drug release profiles. (A) A semi-quantitative *S. aureus* growth inhibition for release solution from NFs (blended or coaxial core-sheath) with/without Doxy incorporation at predetermined time points; (B) The cumulative concentration of Dex released from NFs soaking in distilled water up to 218 h. N=3.

Conclusions: Coaxial core-sheath NF scaffolds are capable of providing controllable and sustained drug release. The therapeutic efficacy of these NF scaffolds in vivo for the implant osseointegration warrants further investigation.