

## Research Article

# Emulsion Electrospinning for Drug Delivery: Two Encapsulation Methods

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## Abstract

One major technique to fabricate core-shell fibers is emulsion electrospinning due to its simple setup and potential to preserve the bioactivity of a loaded agent within the core. Here, we explore two different emulsion electrospinning approaches to encapsulate a hydrophilic drug, as Lidocaine Hydrochloride (LidHCl), inside a hydrophobic polymer fiber, as Poly-Lactic Acid (PLA) in a core-shell structure. Therefore, we incorporate the drug in the fiber core by means of an aqueous phase containing or lacking a polymeric matrix Polyvinyl Alcohol (PVA) to disperse the drug. We studied the electrospinnability of PLA-based emulsion solutions to produce LidHCl-loaded smooth fibers by varying the applied voltage and the tip-to-collector distance. We evaluated the morphology and chemical properties of emulsion electrospun fibers by field emission scanning electron microscopy, transmission electron microscopy and X-ray photoelectron spectroscopy. Finally, we analyzed the drug release profile of both core-shell structures and compared them with blend PLA-LidHCl fiber system. Analysis revealed that emulsion electrospun nanofibers were able to encapsulate the drug within the fibers in both cases. However, PVA matrix inside the core played a key role on the encapsulation and spatial distribution of the drug and therefore on its release. Results suggest that the *in vitro* release profile of a hydrophilic drug could be tailored by the presence of the inner matrix polymer enabling the production of electrospun fibers with desired features.

**Keywords:** Emulsion Electrospinning; Drug Delivery; Core-Shell; Lidocaine Hydrochloride; Polyvinyl Alcohol

## Abbreviations

EDS: Energy Dispersive X-ray Spectroscopy; HPLC: High-Performance Liquid Chromatography; Lid HCl: Lidocaine Hydrochloride; MW: Molecular Weight; PBS: Phosphate Buffer Solution; PCL: Poly (L-Lactic Acid-co- $\epsilon$ -Caprolactone); PLA: Poly-Lactic Acid; PVA: Poly Vinyl Alcohol; SEM: Scanning Electron Microscopy; SPAN 80: Sorbitan Monooleate; TEM: Transmission Electron Microscopy; W/O: Water in Oil; W: Water; XPS: X-ray Photoelectron

## Introduction

Electrospun polymer nanofibers are suitable of serving as tissue engineering scaffolds [1-3]. To provide diverse functionalities and enhance its biological performance, drugs or biomolecules are usually incorporated in the fiber mat. Heparin and vascular endothelial growth factor were loaded on electrospun poly (l-lactic acid-co- $\epsilon$ -caprolactone) (PCL) fibers to improve blood compatibility and cell proliferation [4], while doxorubicin was added into a PCL-poly (ethylene glycol) electrospun system in order to study its antitumoral efficacy [5]. Several antibiotics such as dioxanone [6], ciprofloxacin [7,8], gentamicin sulphate [8] and amoxicillin [9] were loaded on polymer fibers to eradicate infection and thus create a bacteria-free environment favorable to tissue regeneration in wound dressings. High loading capacity, high encapsulation efficiency, simultaneous delivery of diverse therapies, ease of operation and cost-effectiveness are appealing features for electrospinning use in drug delivery [10,11].

In general, two designs can be distinguished for loading a compound in the electrospun polymeric system: (a) matrices and (b) capsules. In the matrix-type structure an active agent dispersed along the whole fiber is achieved by direct blend of the substance with the polymeric solution. In contrast, for capsule-type structure, the therapeutic agent is enclosed in a polymer coating, forming a core-shell fiber. Drug molecules in the core can be either in a pure state form surrounded by a continuous polymer shell or dispersed in a polymeric matrix conforming the core and the whole dispersion system surrounded by a polymer shell [12]. When a drug is mixed with a polymer in an organic solvent, an adequate drug distribution within the electrospun fibers is rarely achieved, as most of the drug remains either near or on the surface of the fibers and a burst release is finally observed [13-15]. Also, loading biomolecules results in a challenge since biological agents may lose their activity in contact with organic solvents [15]. Therefore, capsule-type polymeric delivery systems with a core-shell structure may be preferable for the incorporation of bioactive agents since they allow the use of water as a solvent instead of hazardous chemicals [16]. Co-electrospinning and emulsion electrospinning are usually used to produce this kind of fibers. The former requires two polymer solutions to be fed through a double-compartment nozzle and two separate syringe pumps. This makes co-electrospinning setup more complex than the one used for emulsion electrospinning, which involves only the traditional setup comprising a single nozzle and one pump. By dissolving biomolecules or hydrophilic drugs in the water phase, they can be well incorporated in a Water-in-Oil (W/O) emulsion and protected from the organic

solvents [14,17]. In W/O emulsions the outer layer of the fiber solidifies more rapidly than the inner core because the organic solvent evaporates relatively faster than water and the viscosity of the organic matrix increases more rapidly than that of the droplets [18,19]. So, an inward movement of drops, with the possibility of merging themselves in the core is produced due to the viscosity difference between the drop and the matrix.

Few researchers attempted to produce nanofibers with core-shell structure using emulsion electrospinning [12,17,20]. Xu used an anticancer drug dissolved in an aqueous phase while the oil phase was a chloroform solution of either PLLA or amphiphilic poly (ethyleneglycol)-poly (l-lactic acid) diblock copolymer [20]. No drug crystals were detected on the fiber surface and a sustained release was achieved indicating that the drug was distributed inside the fibers. Also, ketoprofen, an anti-inflammatory drug, was loaded in an emulsion electropun PCL/gelatin system and was further compared with the PCL keptofren-loaded fiber fabricated by direct blend. Results showed that the PCL/gelatin mat significantly hindered drug burst release and exhibited a sustained release capacity for up to 4 days [21]. Spano demonstrated that various species as magnetic nanoparticles, quantum dots and biological molecules, could be introduced within an aqueous phase into an organic phase to form an emulsion without altering the structure and degradation of the fibers [22]. The release profile of the molecules embedded in the aqueous component indicated that the degradation time was proportional to the amount of the aqueous phase and polymer, depending strictly on the blend composition. In this paper, we present nanofibers with a core-shell structure prepared by emulsion electrospinning. Two different fabrication approaches are compared: (a) loading the drug in a pure water phase and (b) loading the drug in a polymeric water phase, prior mixing with the oil phase. PLA was selected as shell material due to its biodegradability, while PVA was added into the polymeric water phase. The model drug used is Lidocaine Hydrochloride (LidHCl), which has anesthetic and antibacterial properties [23]. To the best of the authors' knowledge, a comparison between the two ways of fabricating capsule-type PLA nanofibers has not been reported. Figure 1 shows a schematic diagram of the study here proposed. The blend and the two capsule-type configurations described previously can be seen at the right of the figure.

## Experimental

### Chemicals and Materials

Poly-lactic acid grade 4060D was purchased from Nature Works LCC and Fluorescein dye (AGR1712) was purchase from Agar Scientific (England). Chloroform (analytical grade), toluene (analytical grade) and lidocaine hydrochloride were purchased from Sigma Aldrich (England); the latter one was chosen as the model drug. Also, poly-vinyl alcohol was purchased from Sigma Aldrich (England) with an average molecular weight (Mw) of 70.000 g/mol. Sorbitan monooleate (SPAN 80) a lipophilic emulsifying liquid agent was added as a surfactant into the outer polymer solution prior to emulsification to lower down the surface tension of the oily phase. Moreover, for High-Performance Liquid Chromatography (HPLC) assay acetonitrile was bought from Fisher Scientific and used as the mobile phase whereas a Gemini 5um C18 (250 mm × 4.6 mm) column was purchased from Phenomenex UK. Materials were used

without further purification.

### Emulsion Preparation

Two PLA solutions at concentration of 8% and 10% w/v were prepared by dissolving PLA in a mixture of chloroform and toluene at volume ratio of 7/3 v/v. PLA was weighted and magnetically stirred in the solvent mixture until complete dissolution was achieved. Then 1% w/v SPAN 80 was added to the solution. PLA solutions were used as the oil phase, while two aqueous solutions were used as aqueous phase. The first aqueous solution was prepared by dissolving LidHCl (10% wt based on the polymer weight) in a 5% w/v PVA aqueous solution. The second aqueous solution was made by dissolving the same amount of LidHCl in pure deionized water. Subsequently, 10% v/v of the aqueous phase was mixed with the oil phase, as follows: (a) The aqueous solution with the PVA and LidHCl was added to the oil phase prepared with 8% w/v PLA to form the sample systems PLA-PVA (capsule matrix-type) and (b) the aqueous phase with only the drug (no PVA) was added into the oil phase with 10% w/v PLA, to form the sample system PLA-W (capsule-type). Uniform emulsions were achieved by using an Ultra Turrax IKA T 10 mixer (IKA, Germany) with a working speed rate of 30,000 rpm for 2 minutes followed by a 5-minute sonication using a Branson Digital Sonifier 450 at 10% of maximum power. The PVA solution 5% w/v was prepared in distilled water at 80°C. Pure PLA solution was prepared by dissolving 12.5 wt% of PLA in the same chloroform/toluene solvent system.

**Electrospinning of nanofibers:** Water-in-oil emulsions were fed into 10 ml standard syringes attached to a 20G blunted stainless steel needle using a syringe pump (Harvard Apparatus) set at 1 ml/h flow rate. Fibers were electrospun under different voltages from 10 kV to 20 kV produced by a high voltage source (Glassman High Voltage Inc.), and were collected on an aluminium foil-wrapped collector kept at two different distances at a horizontal orientation. Electrospun PLA blended nanofibres were used as a control sample. All experiments were performed at room temperature. Table 1 shows the different electrospinning parameters applied in the electrospinning process.

### Characterization of electrospun nanofibres

**Scanning electron microscopy:** Field Emission Scanning Electron Microscopy (FEG-SEM, LEO 1530VP) with an accelerating voltage of 5.0 kV was used to observe the fiber morphology of the electrospun membranes after coating each sample with gold/palladium for 2 minutes (SC7640, Emitech). The effect of electrospinning parameters was investigated. Nanofibres mean diameters were measured using image software (AxioVision Rel 4.8) and 150 measurements for each sample.

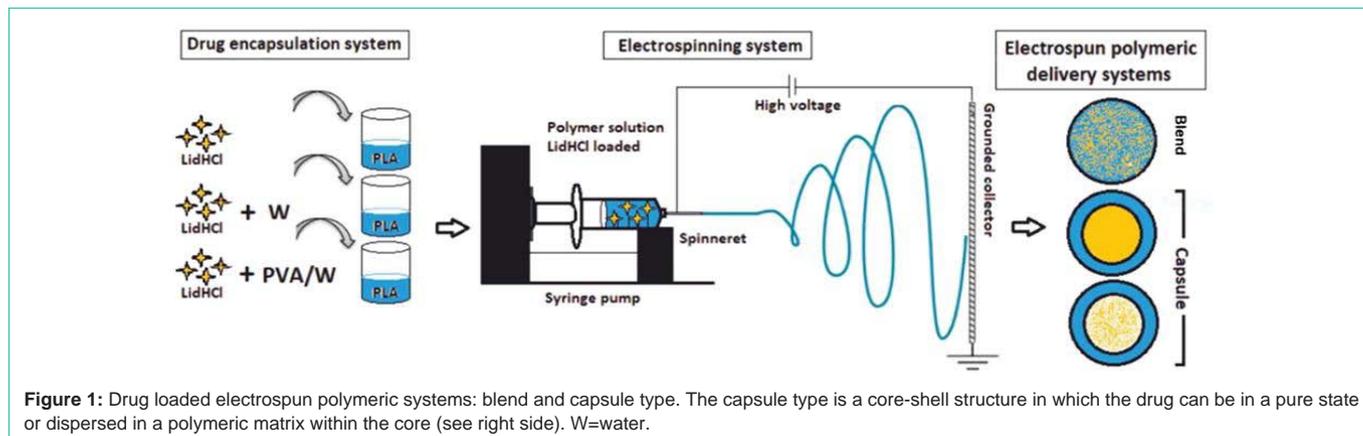
**Transmission electron microscopy:** Transmission Electron Microscopy (TEM) (JEOL-2000FX), with an accelerating voltage of 100 kV, was used to investigate the formation of a core-sheath type structures. Fibers were electrospun directly on cooper grids which were subsequently carbon-coated by sputtering (Q150T ES, Quorum).

**X-ray photoelectron spectroscopy:** To examine the surface chemistry of the fibers, X-ray Photoelectron (XPS) (Thermo Scientific K-Alpha) spectroscopy was used. XPS spectra were obtained by irradiating the material with a beam of X-rays while simultaneously measuring the kinetic energy and number of electrons that escape

**Table 1:** Electrospinning conditions of PLA-PVA and PLA-W emulsion nanofibers systems loaded with 10%wt LidHCl and electrospun at 1 ml/h.

10% LidHCl PLA-PVA*										10% LidHCl PLA-W*									
10		12.5		15		17.5		20		10		12.5		15		17.5		20	
10	15	10	15	10	15	10	15	10	15	10	15	10	15	10	15	10	15	10	15

(\*) Second row values represent the kV applied and third row the tip-collector distance in cm set at the electrospinning.



from the top 1 to 10 nanometers of the material being analyzed.

### In vitro Drug Release Studies

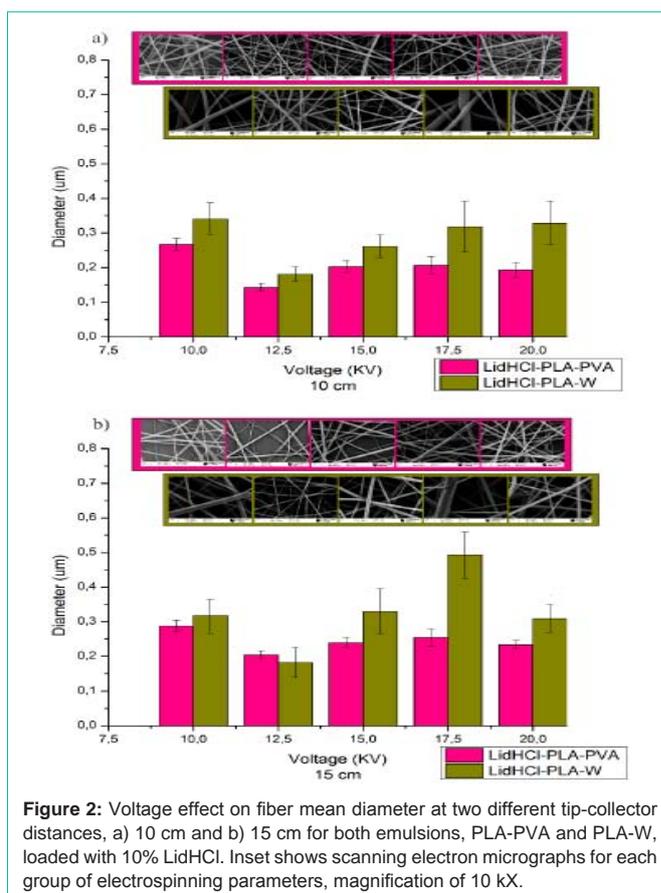
Circular samples of 1 cm in diameter were cut for in vitro drug release study. Each sample was weighted and incubated in sealed vessels filled with 1 ml Phosphate Buffer Solution (PBS) pH 7.4. Experiments were carried out at 37°C and 100 rpm oscillation for a period of 48 hours. The scaffold remained completely immersed without additional support throughout the experiment. At appropriate intervals, an aliquot of 0,7 ml was removed for analysis and replaced with an equal volume of fresh buffer solution. The withdrawn buffer was analyzed using high performance liquid chromatography with HPLC Agilent 1100 series equipment. The mobile phase was a solution of acetonitrile and pure water in a gradient ratio of 12.5% and 87.5%, respectively. Autosampler vials of 2 ml volume were used. The flow rate of 1ml/h and a column temperature of 25°C were kept constant. LidHCl molecule was detected by a diode array detector with the wavelength set at 210 nm.

A calibration curve was performed using LidHCl concentrations ranging from 1 ug/ml to 100 ug/ml in a buffer from a stock solution of 1 mg/ml. Each standard solution was analyzed to obtain a linear profile of known concentrations against the mean area under the curve of the integrated lidocaine peak. These values were plotted using linear regression analysis ( $R^2=0,9$ ) which showed very good agreement with the data points.

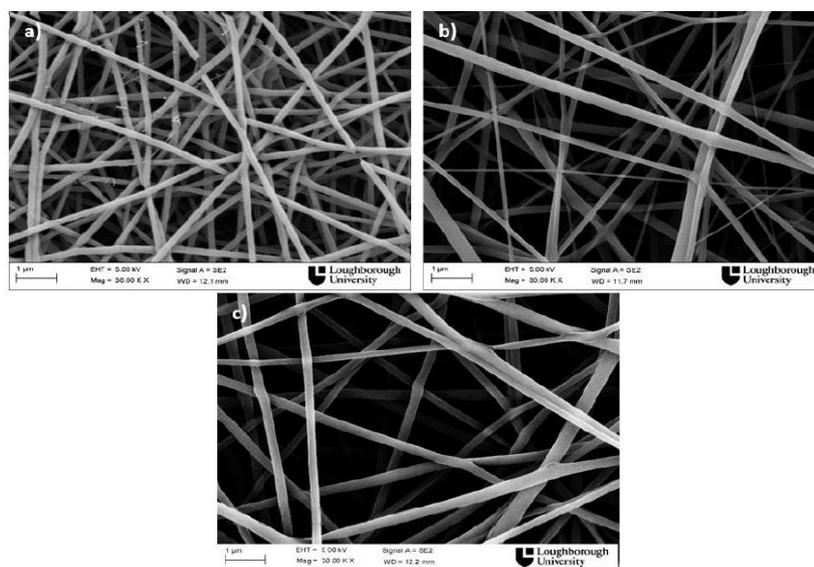
## Results and Discussions

### Optimization of Polymer Concentration

The aqueous phase content was set in 10% of the oil phase and different ratios of PLA in chloroform/toluene solution system were tested until smooth and continuous fibers were collected. Polymer concentration is directly associated with the degree of chain entanglement and furthermore influences the solution viscosity [24]. When low viscosities solutions are electrospun, they are not able to match the electrostatic and columbic repulsion forces that stretch the electrospinning jet due to their own low viscoelastic force causing the



jet to partially break up. Also, under the effect of surface tension, the high numbers of free solvent molecules in the solution come together into a spherical shape causing formation of beads [24,25]. When higher concentrations are electrospun, the increase in viscosity causes an improvement in the viscoelastic force preventing jet breakup. This increased polymer chain entanglement enables the solvent molecules



**Figure 3:** SEM images of electrospun emulsions loaded with 10% of drug. a) control LidHCl-PLA blend sample showing the drug located on the fiber surface and between them, b) LidHCl-PLA-PVA fibers and c) LidHCl-PLA-W fibers.

to be distributed over the polymer molecules leading to the formation of smooth fibers with improved uniformity [26]. Moreover, highly concentrated solutions encounter some problems i.e. droplets drying out at the tip producing a spinneret clogging before initiation of the jet (due to high solution viscosity), hence stopping electrospinning [27]. Therefore, for our experiments, we chose the lowest polymer concentration that prevents the breakup of the polymer into droplets and allows the formation of smooth defect-free fibers.

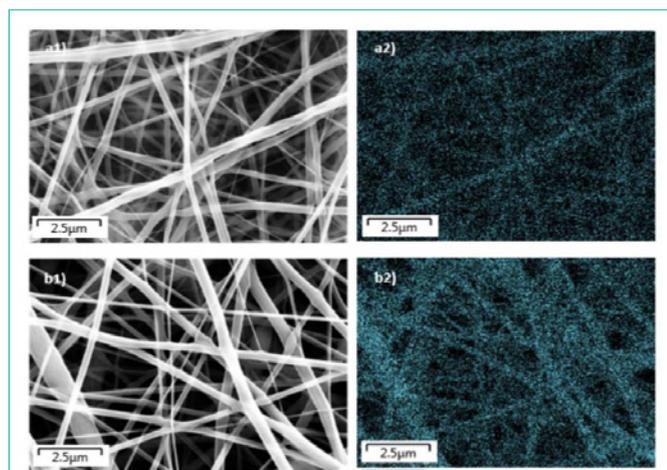
For the system PLA-PVA, 8 wt % PLA was used since lower concentrations produced an undesirable spray-type collection of short-beaded-fibers mixed with droplets. When testing this concentration for PLA-W system, the stated problem appeared suggesting the polymer concentration was not high enough, mainly because only water and no PVA was included in the aqueous phase. Hence, the final concentration of PLA-W chosen for the emulsion electrospinning was 10 wt% PLA. To electrospin LidHCl-PLA control sample (not emulsion type), PLA concentration had to be raised to 12.5 wt % so to collect defect-free fibers. This is in accordance with literature since emulsion electrospinning imparts appropriate rheological properties to low molecular weight polymers or diluted solutions [3,28]. For further analysis, the systems described were loaded with 10% LidHCl/polymer by mass.

## Electrospinning

**Effect of Electrospinning Parameters:** Optimum electrospinning conditions were investigated by varying the voltage and tip-collector distance and analyzing the morphology and diameter distribution of collected fibers. The temperature and relative humidity in the electrospinning chamber were 25°C and 47%, respectively. The type and concentration of surfactant (SPAN 80 at 1% w/v) was selected considering the literature [28]. Defect free and smooth fibers were obtained for all the examined electrospun parameters indicating that the applied voltage and tip-collector distance (within the studied range) were not major factors affecting nanofibers morphologies.

SEM images, shown in Figure 2a and 2b insets, present a similar topography for both types of emulsion fibers electrospun at different parameters. To study the effect on fiber diameter, 150 nanofibers of each sample group were studied and results are summarized in Figure 2. Moreover, a trend can be seen for both electrospun systems; fiber diameter decreases initially with an increase in the applied voltage reaching the minimum and then diameter increases when the applied voltage is increased further. This behavior was previously reported [29,30]. Baumgarten electrospun a polyacrylonitrile solution and evaluated the effect on fiber diameter when applying a voltage ranging from 5 kV to 20 kV. He discovered that the relation was not monotonical and the lowest fiber diameter of 230 nm was found to occur within voltages of 10 kV to 12.5 kV [29]. In the current work, the optimal voltage for minimum fiber diameter arises from the balance of the electrical drawing force and the solvent drying rate. When these conditions are achieved, fibers not only show minimum diameter but also their narrowest diameter distribution.

For a tip-collector distance of 10 cm (Figure 2a) and 15 cm (Figure 2b), it can be observed that PLA-W emulsion fibers have higher diameters comparing to PLA-PVA. This could be attributed to the higher polymer concentration in PLA-W compared to PLA-PVA emulsion. An increase in polymer concentration results in a higher chain entanglement along with an increase in solution viscosity and viscoelastic force that limit the stretching effect of the electrostatic and columbic repulsion forces, hence, resulting in thicker fibers [25,30]. Emulsion fiber diameters varied from 140 nm to 500 nm. The narrowest fibers were obtained at 12.5 kV for all samples being LidHCl-PLA-PVA fibers the ones presenting the lowest mean diameter (142 nm ± 12 nm) for a tip-collector distance of 10 cm. Also, a narrower diameter distribution is observed for capsule-matrix (PLA-PVA) fiber type compared to PLA-W, which could also be closely related to the polymer concentration. Similar behavior was observed by Gu and Ren in PLA electrospun nanofibers [31]. They demonstrated that fibers with lower variation in diameter



**Figure 4:** Micrographs and EDS maps of nitrogen. Pattern match between emulsion electrospun fibers and N distribution confirming the presence of the drug in LidHCl-PLA-PVA fibers (a1, a2) and LidHCl-PLA-W fibers (b1, b2), respectively.

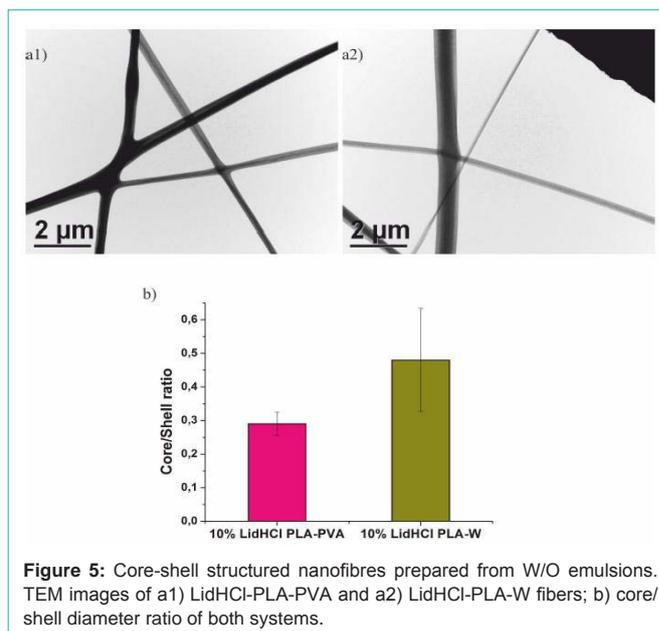
can be obtained at lower concentration regardless of applied voltage.

Stable electrospinning conditions were chosen to carry out additional studies on nanofibres mats, this is: no droplet dripping, stable Taylor cone formation at the tip of the needle and continuous jet ejection during the emulsion electrospinning process. Therefore, 15 kV and 10 cm were set as electrospun parameters for further studies, Figure 3 shows micrographs of blend sample and W/O emulsion fibers loaded with 10% of LidHCl.

Drug particles located on the fibers surface of blend LidHCl-PLA mats can be seen in Figure 3a. This is mainly due to the hydrophilic nature of LidHCl which could not be dissolved in hydrophobic PLA/chloroform-toluene system. Results are in accordance with literature [20]. Contrarily, when LidHCl was dissolved initially in water and subsequently incorporated into the organic solvent, the drug seemed to be perfectly encapsulated inside the electrospun fibers and no drug particles were observed on the surface, see Figure 3b and 3c. Regarding the mean nanofiber diameter, the values for each system are  $210 \text{ nm} \pm 22 \text{ nm}$ ,  $202 \text{ nm} \pm 19 \text{ nm}$  and  $261 \text{ nm} \pm 42 \text{ nm}$  for blend LidHCl-PLA, LidHCl-PLA-PVA and LidHCl-PLA-W, respectively. Here on we will refer as LidHCl-PLA-PVA to the capsule-matrix type fibers and as LidHCl-PLA-W to the capsule type fibers, both loaded with 10% of the drug.

### Drug loading characterization

Chemical characterization by Energy Dispersive X-ray Spectroscopy (EDS) was used to confirm the presence of the drug in the fibers. Figure 4a1 and 4b1 show the scanning electron micrographs obtained from LidHCl-PLA-PVA and LidHCl-PLA-W fibers, respectively. The EDS elemental maps of Nitrogen (N) from the showed area in the left, are presented using blue dots in Figure 4a2 and 4b2. Blue spots confirm LidHCl dispersion throughout the polymeric membranes, also it is evident that N signals distribution matches the fibers alignment. It is possible to see a difference in the N arrangement when comparing the fibers in both emulsion samples. Nitrogen dots, in PLA-PVA samples seem to be more distributed along the fiber and less brighter compared to PLA-W fibers, where



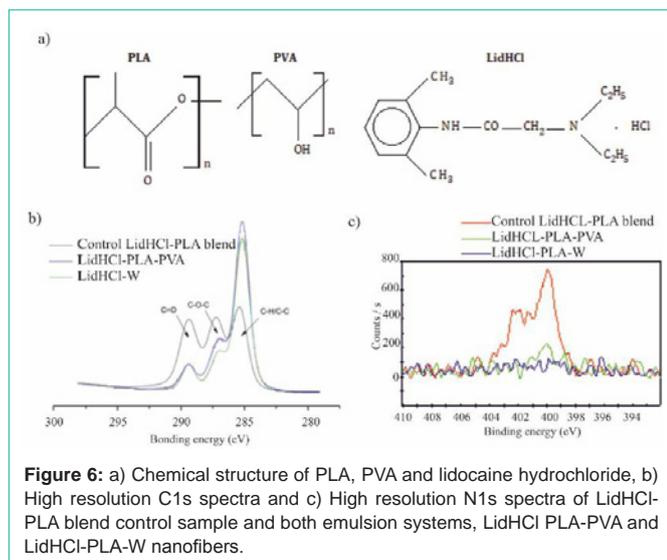
**Figure 5:** Core-shell structured nanofibres prepared from W/O emulsions. TEM images of a1) LidHCl-PLA-PVA and a2) LidHCl-PLA-W fibers; b) core/shell diameter ratio of both systems.

the N dots are closer to each other and reveal higher intensity. This could be related to the presence of the PVA in the first sample which creates a polymeric matrix that encloses the nitrogen attenuating its signal and allowing a homogeneous spatial distribution of the drug along the matrix. On the other side, PLA-W fibers show a brighter and higher density of N dots considering there is no polymeric matrix within the core to pack the drug. Nitrogen is only present in the chemical structure of LidHCl; hence this pattern match further confirms the incorporation of LidHCl into emulsion electrospun fibers. It is important to realize that due to the resolution depth of EDS technique, generally  $1 \mu\text{m}$ , it is not possible to conclude whether the drug rests on the surface or inside the fibers.

TEM images reflect a two-phase structure for both samples, see Figure 5. A difference of electron transparency properties due to the presence of the drug within the water phase confirms the formation of core-shell structures. The inner dark regions correspond to the higher electron density of chloride counterions of lidocaine loaded in the water phase and the outer light regions are identified as the PLA. The aqueous phase is restricted to the central part of the PLA fiber due mainly to the immiscibility of the two fluids. The inner component was properly wrapped in the center of nanofibres for both electrospun systems: LidHCl-PLA-PVA and LidHCl-PLA-W (see Figure 5a1 and 5a2, respectively); though a few cases of irregular movement of the inner component to one side of the fiber were seen.

The relationship between core and shell diameters was assessed for 50 fibers. Figure 5b shows the core/shell diameter ratio for LidHCl-PLA-PVA and LidHCl-PLA-W systems. A lower core-shell diameter ratio and narrower distribution for LidHCl-PLA-PVA can be explained by PVA, which confers higher viscosity and lower evaporation rate to the aqueous phase.

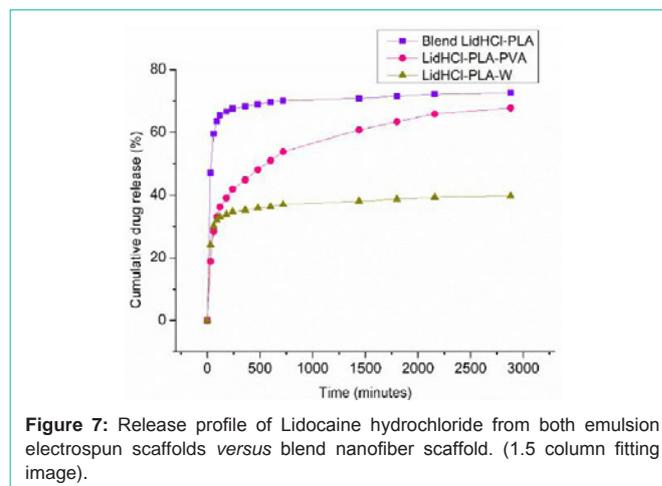
To confirm LidHCl encapsulation inside the nanofibers, the surface mat chemical composition was assessed by XPS. As expected, there are C1s and O1s peaks presented at binding energies of 285 eV and 533 eV, respectively. Moreover, the peak area ratio was also found



to be in good agreement with the theoretical values of O/C in PLA. In Figure 6a, the chemical structure of PLA, PVA and LidHCl can be seen. Figure 6b shows the C1s spectra of the PLA emulsion fibers of capsule-matrix type and capsule type as well as the control sample of LidHCl-PLA blend. The spectra of all the samples show peaks at 289 eV, 287 eV and 285 eV corresponding to carbon atoms participating in C=O, C-O-C and C-H/C-C bonds, respectively. Moreover, a slight shift on C-H/C-C bonding atoms peak of the control sample respect to the emulsion electrospun fibers can be observed. This could be due to the presence of C-N bond with an energy peak of 286 eV which perfectly fits in the plot, shifting the C-H peak from 285,18 eV to 285,38 eV, condition not seen in the emulsion samples spectra. Control blend sample presents high signals at binding energy between 398 eV to 403 eV in the survey XPS spectrum corresponding to characteristic N1s peak which reveals the presence of nitrogen. When analyzing emulsion samples at this energy interval it is possible to see that LidHCl-PLA-PVA samples present a small peak at 400 eV which is assigned as well to the presence of N atoms in the surface of the sample, contrarily to LidHCl-PLA-W which does not present any peak at this energy gap.

Nitrogen atoms are only present in the chemical structure of LidHCl. For this reason, the appearance of a peak corresponding to carbon atoms participating in C-N bonds in C2s spectrum, as well as of a peak attributed to nitrogen atoms in the survey XPS spectrum is an evidence of the presence of LidHCl in the surface membrane of control sample. As well, the peak at 400 eV presented for LidHCl-PLA-PVA samples confirms that part of the drug was placed in the surface of the fibers. Figure 6c shows high resolution spectra for N1 peak. These results suggest that LidHCl is properly wrapped in PLA-W core-shell samples, and the shell thickness is at least beyond the ultimate detection depth of XPS, i.e., 5 nm to 10 nm.

The physical-chemical Characterisation of emulsion electrospun fibers allows understanding the behavior of the encapsulated drug in the polymeric delivery vehicle. The presence of PVA as a core material has shown to act as a mechanical support of the drug allowing a homogeneous distribution along the fiber. Moreover, the small N peak detected by XPS on LidHCl-PLA-PVA fibers suggests



that a small part of the drug was found on the surface. This could be related to the miscibility between PVA and PLA, which could allow partial migration of LidHCl to the organic phase during preparation of the emulsion [32].

### Drug Delivery

*In vitro* release profile of LidHCl from capsule-matrix type and capsule type emulsion electrospinning nanofibres were studied in PBS (pH 7.4) to evaluate the potential application of LidHCl loaded nanofibres as drug delivery systems. Control sample release profile was also plotted for comparative purposes. The cumulative release curves of the drug loaded nanofibres are shown in Figure 7 where y-coordinate represent cumulative percent drug release and x-coordinate represents drug release time points.

LidHCl blend samples eluted the drug in a burst-release fashion, with 65% of LidHCl detected in the first hour followed by a plateau. This was shown previously by Thakur and co-workers for a similar blend system [33]. Hydrophilic drugs exhibit a tendency to migrate towards the jet surface during electrospinning, hence drug surface enrichment is commonly observed and therefore greater release [34].

Over time LidHCl loaded by emulsion electrospinning was released much more slowly than the drug in the typical blend system. The core-shell nanostructure significantly alleviated the initial burst showing a drug release of 35% for both emulsion systems after 60 minutes. This confirms a proper encapsulation process during the emulsion preparation in which drug molecules were wrapped by surfactants and polymers. After this point in time, LidHCl-PLA-PVA samples showed a sustained and gradual increase in the release pattern achieving more than 70% of cumulative release after 3000 minutes. A different biphasic profile was revealed for LidHCl-PLA-W fibers, whereas, after the initial rapid release, a sustained and minor release reaching less than 40% was seen for the same period. This suggests that the remaining drug in the system LidHCl-PLA-W is more efficiently encapsulated in the inner core hence the low and stable release profile along the entire period.

In our core-shell fibers, PLA hydrophobic polymer shell separates the drug from the outer aqueous medium and hinders the entry of the dissolution medium into the nanofibers hence protecting the drug from scaping suddenly to the system.

However, regarding XPS results were PLA-PVA mats showed the presence of N in the first 10 nm layer of the fiber and considering that these fibers express a similar first-stage release as PLA-W mats, it can be inferred that the drug is not strictly in the surface but also dispersed in the PLA shell matrix. This suggests that LidHCl dissolved in the core fluid could have diffused across the core-shell liquid interface during the electrospinning process. PVA seems to homogenize the drug distribution in the core and due to its miscibility with PLA, PVA would partly allow the presence of LidHCl among the shell, allowing a more sustained and gradual drug release. This could be the evidence that the presence of an inner polymer as PVA plays a key role on the drug release profile of the core-shell system by imparting a compatible environment between the core and shell materials, which may help with the long-lasting anesthesia effect.

## Conclusion

Two different approaches for emulsion electrospinning fabrication were investigated for the incorporation of LidHCl and compared with direct blend of the drug in PLA. Firstly, the drug was dissolved in an aqueous medium which was later mixed with the organic PLA phase to form an emulsion. The presence of PVA in the aqueous phase was studied along this work. Core-shell nanofibers were electrospun efficiently with both emulsion combinations. LidHCl could not be homogeneously distributed in direct blending electrospun fibers due to its poor dissolution properties in organic solvents. Nevertheless, emulsion electrospun fibers were successful to load the drug within the nanofibers by encapsulating the LidHCl. The presence of PVA in the aqueous phase acts as a matrix that helps on the internal drug distribution along the whole fiber, allowing a more controlled and stable release overtime. Thus, capsule-matrix fibers could be a prospective vehicle for drug delivery in tissue engineering applications.

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