Coaxial electrospun membranes of poly($\varepsilon$-caprolactone)/poly(lactic acid) with reverse core-shell structures loaded with curcumin as tunable drug delivery systems

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Abstract
Nano fibrous membranes core-shell of poly(lactic acid) (PLA) and poly($\varepsilon$-caprolactone) (PCL), encapsulating 1 wt% of curcumin, are fabricated by coaxial electrosprning technique. Morphology and physical properties, as well as the release of curcumin, are studied and compared with neat PLA and PCL individually spinned. Morphological analysis shows for all the samples the obtainment of fiber oriented in random way, without defect and with a narrow distribution of the fiber dimensions (344 nm for PCL fibers and 450 nm for PLA fibers). Mechanical performances and barrier properties are evaluated on all membranes and found to be dependent on the fibers' composition and morphology. Water contact angle for all membranes is found higher than 90° (from 103° for PLA-Curc to 128° for PCL-Curc), expected since the hydrophobic behavior of the micro/nano electrospun morphology. The curcumin release from the coaxial fibers, modeled with a modified Weibull equation, shows the possibility of a fine tuning of drug release (up to 15 days) for the produced materials, depending on the required application.

KEYWORDS
coaxial electrospinning, controlled release, curcumin, drug delivery

1 | INTRODUCTION

Electrospinning is emerging more and more as an interesting technique for producing nano and micro polymeric fibers for targeted applications.1-4 In fact, the electrospun fibers show fitness in diversified technological fields such as wound healing, gas shielding, filtration, protective clothing, and tissue engineering applications.5-7 In particular, the use of electrospun fibers is highly promising as for scaffolds for biomedical and drug delivery applications.8,9 Among all, the high active compound loading capacity, high surface area, simultaneous delivery of different therapeutic agents, good mechanical strength, and low cost are appealing characteristics to be applied in drug delivery systems.10,11 Delivery devices obtained from electrospun membranes for controlled drug release are under deep investigation aiming of overcoming several limitations of traditional administration routes. Drugs are encapsulated in electrospun fibers, from which the drugs are released in a controlled way. The advantages of this novel drug delivery system over traditional methods are multiple. Above all, release rates can be designed in order to fulfill the needs of a targeted application. Some diseases need to be treated by guaranteeing a controlled drug concentration, which may require to tailor the release rate of drug delivery. Furthermore, controlled release systems, through encapsulation, supply protection of drugs which could undergo a fast inactivation in the patient body. Further technological development has been recently obtained by the coaxial electrospinning, that provides noticeable and unique features relevant for biomedical applications.12-15 This methodology exploits a
co-annular nozzle that emits the core layer from the inner nozzle and the shell polymer from the outer nozzle. As a consequence, this recent technology is able to combine characteristics of different polymeric systems into a single core/sheath fiber. For long-term drug delivery implants major benefits of coaxial electrospinning are related to the possibility of tailoring the drug release working on many parameters: (i) encapsulation of different functional molecules in a simple one-step process; (ii) controlling the drug location, either in core or sheath layer; (iii) changing the drug concentration; (iv) modulating the fibrous material, as well as the layer thickness. In particular, the use of two different materials can help to tailor the release times, since the drug release can be controlled by some phenomena such as erosion or diffusion. The dominant release mechanism will in turn affect the drug pharmacokinetics, crucial in determining drug performances. Compound release from biodegradable polymers in vivo is generally affected by an overlapping of both mechanisms, and, so, is based on the rates of erosion and diffusion. Coaxial electrospinning technology has gained interest as a new technique for fabricating core-shell systems for a controlled drug release such as poly(butylene succinate)-polyethylene glycol loaded with curcumin, polyethylene oxide-(silk/collagen) for the release of flurbiprofen or gelatin-polycaprolactone encapsulating metronidazole. This paper reports, then, the preparation of coaxial membranes as tunable delivery systems of curcumin, as anti-inflammatory agent. Two biodegradable polymers, poly(ε-caprolactone) (PCL) and poly(lactic acid) (PLA) were used for shell and core alternatively. PCL and PLA, which possess no toxicity, are tissue-compatible materials with the vital organs and therefore used in drug delivery devices, remaining active for long times. Indeed, they are characterized by very different degradation times, and therefore the competition between diffusion and erosion mechanisms can help tailor the release depending on the necessity. Here we used Curcumin, (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), that is the main active component isolated from rhizome of Curcuma longa as a model active agent, both in the core of either PCL or PLA, as a first-line investigation of the release properties by the two materials in coaxial membranes, compared to the pure polymers. Despite the health-beneficial effects, the poor bioavailability and in vivo instability of curcumin limit its therapeutic efficacy. We compared the electrospun fiber morphology and physical properties (i.e., thermal, mechanical, barrier) of pure PCL and PLA loaded with curcumin and the coaxial fibers having PCL and PLA either in the core or in the shell and curcumin in the core. Controlled release in vitro of curcumin was also analyzed by applying a modified Weibull model which allowed for taking into account the double step release.

2 | EXPERIMENTAL

2.1 | Materials

Poly(ε-caprolactone) (PCL molecular weight of 80,000 Da) was purchased from Sigma Aldrich while poly(l-lactide-co-ε-lactide) (PLA 4032 D-Mw = 160,000 g/mol) was purchased from NatureWorks (Minnetonka-Minnesota). N,N-dimethylformamide (DMF-CAS 68-12-2) and Tetrahydrofuran (THF pure-CAS: 109-99-9) were purchased from Sigma-Aldrich. Ethanol (EtOH purity >96%-CAS 64-17-5) and phosphate buffer solution (PBS) pH = 7 ± 0.02 (CAS: 7558-79-4) were purchased from Carlo Erba Reagents (Cornaredo-Milano). Curcumin (Curc) were purchased from Sigma-Aldrich (Milan, Italy) in powder form.

2.2 | Fabrication of curcumin-loaded membranes

The electrospun membranes were produced by dissolving PCL and PLA in a solvent mixture THF/DMF (50:50 v/v) at 12% w/w. Curcumin was added to PCL or PLA solution in order to guarantee a drug to polymer ratio of 0.1: 9.9 (w/w) and mixed for 4 h at 40°C (300 rpm) to obtain a homogenous solution. Hereafter, the membranes obtained from PCL or PLA with curcumin were labeled as PCL-Curc or PLA-Curc.

Coaxial electrospun membranes were obtained by using a coaxial nozzle (EM-CAX-Ime electrospinning). Two separate volumetric pumps were used to process the polymeric solutions, prepared as described before. The curcumin loaded PCL/PLA coaxial nanofibrous mats were processed by coaxial electrospinning; the drug loaded solution constitutes the inner core while the no-loaded solution is the outer shell. The produced composite nanofibrous mats were marked as PCL-Curc/PLA and PLA-Curc/PCL. Before performing the experiment, each solution was fed in a 5 mL syringe pump. The sets of electrospinning conditions are present in Table 1 and optimized to produce beads-free fibrous membranes. Temperature and relative humidity were fixed for all the experiments and equal to 25°C and 35%.

2.3 | Methods

Climate controlled electrospinning apparatus (EC-CLI, IME Technologies, Geldrop, The Netherlands) was used to produce fibrous membranes, set a vertical setup. Core/shell nanofibers were obtained through a coaxial apparatus containing two concentric needles. The diameters of the inner and outer needles were 0.8 and 1.2 mm, respectively. Finally, an aluminum collector was used to collect the electrospun nanofibers.

Scanning electron microscopy (SEM) analysis was performed using a Quanta 200 F microscope in high-vacuum mode. Before the analysis, electrospun membranes were covered with a thin film of gold using an Agar Automatic Sputter Coater (Mod. B7341, Stanstead, UK) at 40 mA for 120 s prior the analysis.

Transmission electron microscopy (TEM) analysis was carried out using a FEI Tecnai 200 kV electron microscope operating at 100 kV. The samples for the TEM observation were directly depositing the electrospun fibers onto the copper grids.

Mechanical properties were evaluated using a dynamometric apparatus INSTRON 4301. Experiments were conducted at room temperature fixing a deformation rate of 5 mm/min. Elastic modulus was
Electrospinning set parameters

| Sample          | Polymer concentration (% w/w) | Voltage (kV) | Distance (cm) | Flow rate (mL h⁻¹) |
|-----------------|-------------------------------|--------------|---------------|------------------|
| PCL-Curc        | 12                            | 18           | 25            | 0.5              |
| PLA-Curc        | 12                            | 25           | 25            | 0.7              |
| Core: PCL-Curc  | Core: 12                      | Core: 25     | Core: 25      | Core: 0.5        |
| Shell: PLA      | Shell: 12                     |              | Shell: 0.7    |                  |
| Core: PLA-Curc  | Core: 12                      | Core: 25     | Core: 0.7     |                  |
| Shell: PCL      | Shell: 12                     |              | Shell: 0.5    |                  |

evaluated in the deformation range of 0.1%. Results were averaged on five samples.

*Barrier properties of water vapor* were estimated through a DVS automated multi-vapor gravimetric sorption analyzer, using nitrogen as a carrier gas at 30°C. Samples were exposed to increasing water vapor activities until saturation and their weight was recorded. The sorption coefficient, *K*, was calculated from *K* = *P/C, where* P is the partial pressure into the gravimetric chamber, and *P* is the saturation water pressure at the experimental temperature. The adsorbed water mass was measured by a microbalance and recorded as a function of time. From the sorption kinetics, it was possible to derive the diffusion coefficient at each activity.

*Water contact angle measurements* were carried out using a high-resolution camera. Droplet of distilled water (100 µL) were let spread onto the fibrous mat. The contact angle was evaluated using Drop Analysis software. Five tests were carried out for each sample.

Release of curcumin was analyzed using a Spectrometer UV-2401 PC Shimadzu (Japan). The tests were performed using rectangular specimens with area 4 cm². The release medium was a solution of PBS/EtOH 70:30 v/v. Each sample was immersed in 25 mL of solution. The solution was stirred at 100 rpm in an orbital shaker (VDRL MOD. 711+ Asal S.r.l.). The release medium was withdrawn at set time intervals and replenished with fresh medium. The detection wavelength was set at 431 nm.

**2.4 Statistical analysis**

Results were expressed as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) and Tukey’s test were used for statistical comparison. Difference was regarded as statistically significant when *p* < 0.05. Coefficient of determination *R²* was used to evaluate the goodness of the fitting processes.

**3 RESULTS AND DISCUSSION**

Electrospinning conditions were firstly optimized to produce fibrous beadless membranes. By adopting the optimal conditions, fibers loaded with curcumin were successfully collected. SEM images and the fiber diameter distributions of the electrospun membranes are shown in Figure 1.

The electrospinning of PLA solution provides randomly fibers oriented without defects, whose average diameter is roughly 450 nm, while the electrospinning of PCL led to fibers without defect too, with narrower fibers diameter distribution (344 nm). Regarding the coaxial systems, the fibers are well formed and almost free of defects. Their dimensions are slightly smaller than the neat polymers and are very similar, being 404 and 411 nm, respectively. In Figure 2(A),(B), the TEM analysis shows the morphology of a single fiber having the PCL-Curc/PLA and PLA-Curc/PCL, respectively.

It is evident that the core, containing the drug, is thicker than the shell of PLA. Actually, the PCL core is 344 nm whereas the PLA shell is 121 nm. Even in this case the core containing the drug is thicker than the shell of PCL. Actually, the PLA core is 267 nm whereas the PCL shell is 149 nm. Therefore, in either case the core containing the drug is thicker than the shell.

The mechanical properties of PLA and PCL fibers and membranes loaded with curcumin, were analyzed through stress–strain curves, and compared to the coaxial fibers, PCL core and PLA core. The mechanical parameters are reported in Figure 3.

The elastic modulus of PCL-Curc is much lower than the one displayed by PLA-Curc, due to the fact that polylactic acid is a stiffer polymer than PCL. The coaxial membranes show a modulus even higher than the neat PLA. This is an indication of a synergistic effect of both polymers respect to the load resistance. At variance, the coaxial systems are less extensible and show a lower stress at the break point, respect to the uniaxial membranes. Specifically, for the elongation at break prevails the effect of the PLA being a material stiffer and less elongable by PCL.

Barrier properties to water vapor were evaluated on electrospun systems. Concerning the biodegradable polyesters, the sorption of water can lead to modification in the polymers chains arrangement (i.e., swelling, plasticization, hydrolysis) since the presence of hydrophilic groups. Being the curcumin a compound with very low affinity to water, it is possible to assume negligible its contribution to the transport properties (S and D) to water. Figure 4 shows the equilibrium concentration of water vapor, *celaide* (g/100 g), as function of water activity (*a_w* = 0.2–0.6) for all the samples.

All samples show an ideal behavior in the investigated partial pressure range, that allowed the evaluation of the sorption coefficient, *S* (Table 2), from Henry’s law (Equation (1)):

\[ C_{eq} = S \times P \] (1)

The estimation of the diffusion coefficient was obtained from the mathematical analysis of diffusion data. Fick’s second law is expressed by Equation (2):
with $m_i =$ initial mass of moisture and $m_{eq} =$ mass of moisture when saturation is reached. For short times (until $m/m_{eq} < 0.55$),

$$\frac{m - m_i}{m_{eq} - m_i} = 1 - \frac{8}{\pi^2} \sum_{j=1}^{\infty} \left( \frac{1}{(2j+1)^2} \right) \exp \left[ - \frac{(2j+1)^2 \pi^2 D t}{d^2} \right]$$  \hspace{1cm} (2)

an approximated form of Equation (2) is represented by Equation (3):

$$\frac{m}{m_{eq}} = 4 \sqrt{\frac{D t}{\pi}}$$  \hspace{1cm} (3)
The evaluation of the slope ($k$) allowed to easily calculate the diffusion coefficient by using Equation (4):

$$D = \pi \left( k \cdot \frac{d}{4} \right)^2$$

(4)

the zero-diffusion coefficient $D_0$ (Table 2) is easily obtained by extrapolating the fitting line at $c_{eq} = 0$.

Figure 5 reports the $\ln(D)$, $D$ in cm$^2$/s, as a function of the equilibrium moisture content ($c_{eq}$, g/g).

It can be stated that diffusion coefficient is quite independent on adsorbed water vapor content in the whole investigated range. It follows that, with a good degree of approximation, the $D_0$ coincides with $D$ at any vapor pressure. It is evident that PCL and PLA show the lower diffusivity parameters, while both coaxial membranes highest values. This could be due to a higher porosity in the coaxial systems that can be responsible of a kinetic of transport of water vapor dominated by a traveling through preferential voids into the structures.

The permeability, the product of sorption and diffusion (Equation (5)), was even reported in Table 2.

$$P = S \cdot D_0$$

(5)

The determination of the contact angle is important in biological systems, since it quantifies the wettabiity of a solid surface by a liquid, in particular the biological liquid circulating locally near the membrane.
As a matter of fact, cells adhesion is supposed to spread more effectively on hydrophilic surfaces rather than hydrophobic surfaces. Moreover, the drug release due to polymer erosion depends on the possibility of water to swell the material favoring hydrolysis reactions. Figure 6 depicts the contact angle of PCL/Curc, PLA/Curc, and the coaxial PCL-Curc/PLA and PLA-Curc/PCL.

The contact angles of the electrospun structures were higher than 100° for all the systems studied. They indicate that the water droplet does not easily spread on the surface since the intrinsic hydrophobicity of the nonwoven organization of the membrane, attributable to the micro/nano fiber morphology, responsible for the strong decrease in the wettability of these materials. In any case PLA fibers maintain lower hydrophobicity than PCL, as expected by the chemical structure.

Controlled and targeted release of drugs is desirable for systemic administration due to some advantages, such as: (i) improving the targeted release and the effectiveness of drug; (ii) reducing the side effects; (iii) decreasing the frequency of administration. Therefore, it is worthwhile investigating the release profiles. Considering that curcumin is not soluble in water, we used artificial biologic fluid (PBS/EtOH 70:30 v/v) mainly to compare the releasing properties from the pure polymers (both PLA and PCL) and from the coaxial systems. The next step will be the investigation of release properties in water, due to the polymer erosion. Figure 7 shows the release of curcumin from pure PLA and pure PCL (a) and coaxial membranes (b), as function of time (h).

It can be seen that the release curves have a very complex behavior, characterized by a first release rapid step (burst), followed by slower stages up to attaining a plateau regime.

The initial burst, characteristic of many controlled-release systems, can be ascribed to many mechanisms, such as surface desorption, pore diffusion, or the lack of a diffusion front barrier regulating the diffusive process. The cumulative drug release was analyzed and fitted through the statistical Weibull model.\(^\text{27}\) The Weibull model, which can be widely applied to many dissolution curves, is expressed in Equation (6):\(^\text{28}\)

\[
\frac{M}{M_0} = 1 - \exp\left(\frac{t}{T}\right)^b
\]  

where \(M\) represents the amount of drug dissolved as a function of time \(t\), \(M_0\) is total released amount of drug, \(T\) parameter is the latency time resulting from the release process, the scale factor \(A\) accounts for the time dependence while \(b\) parameter is related to the drug release mechanism.\(^\text{29}\) The drug release mechanism could be

![Figure 4](image1.png)  
**Figure 4** Sorption isotherms of electrospun membranes

![Figure 5](image2.png)  
**Figure 5** Diffusion coefficients as function of equilibrium concentration \(c_{eq}\) (g/100 g)

### Table 2: Sorption, diffusion and permeability of electrospun membranes

|                  | Sorption parameter \((S)\) \((\text{g/100 g})\) | Diffusion parameter \((D)\) \((10^{-7} \text{cm}^2 \cdot \text{s}^{-1})\) | Permeability \((P)\) \((10^{-4} \text{g/100 g} \cdot \text{atm}^{-1} \cdot \text{s}^{-1} \cdot \text{cm}^2 \cdot \text{s}^{-1})\) |
|------------------|---------------------------------|---------------------------------|---------------------------------|
| PCL-Curc         | 17.18 ± 1.26                    | 3.71 ± 0.26                     | 6.37 ± 0.19                     |
| PLA-Curc         | 15.15 ± 1.54                    | 9.52 ± 1.22                     | 14.4 ± 0.45                     |
| PCL-Curc/PLA     | 21.00 ± 2.12                    | 11.1 ± 1.26                     | 23.30 ± 0.52                    |
| PLA-Curc/PCL     | 9.07 ± 0.95                     | 17.6 ± 3.21                     | 1.60 ± 0.31                     |
schematized as the superposition of different mechanisms of drug transport. At any time, the drug release can be described as the sum of a diffusion-controlled phase followed by a relaxation-controlled phase. A modified Weibull equation could be proposed (Equation 7) considering that the latency time $T$ is usually equal to zero$^{28}$:

$$\frac{M}{M_0} = \theta \left(1 - \exp \left(\frac{t}{b_1} \right)\right) + \left(1 - \theta\right) \left(1 - \exp \left(\frac{t}{b_2} \right)\right)$$

(7)

The first contribution with weight $\theta$ represents the contribution of the diffusion-controlled mechanism while the second contribution $(1 - \theta)$
represents the contribution of the slow release due to polymeric chains relaxation. Figure 7(A) shows the fittings (solid lines) through the Equation (7) of the release data of PCL-Curc and PLA-Curc electrospun membranes over the time range, with Weibull parameters listed in Table 3 with the correlation coefficient ($R^2$).

In order to analyze the multi-stage release kinetics of curcumin from coaxial electrospun membranes, Equation (7) can be further modified by introducing the parameter $t_m$ which accounts for the maximum cumulative drug release time of the stage 1 (Equation 8):

$$\frac{M}{M_0} = \theta \left(1 - \exp^{-\frac{t}{t_m}}\right) + \left(1 - \theta\right) \left(1 - \exp^{-\frac{t_{14}}{t_m}}\right)$$

Figure 7(B) shows the fittings of Equation (8) to the release data of coaxial electrospun membranes over the time range. Evaluated parameter of Weibull model are listed in Table 3. Comparing the release behavior of curcumin from the neat polymer or the same in the core of the coaxial fiber, the quantity from the second is lower than from the first. This is expected since the molecules going out of the core must diffuse into the shell polymer before reaching the external part of the membrane. The same, although in a lesser extent, occurs in the second stage of release.

4 | CONCLUDING REMARKS

Coaxial electrospun membranes of poly($\varepsilon$-caprolactone) (PCL) and poly(lactic acid) (PLA) with reverse core-shell structures loaded with 1 wt% of curcumin as tunable drug delivery systems. The morphology and physical properties were compared with membranes based on PCL and PLA loaded with curcumin at the same percentage. In the coaxial procedure, the drug curcumin was introduced into the core, either PCL or PLA, with the other polymer as shell. Morphological analysis showed for all the samples the formation of randomly oriented, defect-free cylindrical fibers. The neat polymers showed a good homogeneous distribution with average fiber diameter lower for PCL, while the coaxial fibers indicated higher dimensions of the core with the drug, respect to the shell. Mechanical and barrier properties were evaluated on both the coaxial structures and the nanofibrous mats of pure polymers loaded with curcumin, and found dependent on the fibers' morphology and composition. All membranes showed contact angles all higher than 90°, indicating that the micro/nano fiber morphology is the main responsible for the strong reduction of the wettability of these materials and has to be considered for the drug release due also to the erosion of the polymers. The curcumin release from the coaxial fibers, modeled with a modified Weibull equation, resulted slower than the neat polymers, showing the possibility of tuning the release of the drug, depending on the target of the specific application.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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