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Emulsion-coaxial electrospinning: designing novel architectures for sustained release of highly soluble low molecular weight drugs

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Abstract
In drug therapy, most therapeutic drugs are of low molecular weight and could freely diffuse in the biological milieu depending on the administration route applied. The main reason for the development of polymeric drug carriers is to obtain desired effects such as sustained therapy, local and controlled release, prolonged activity and reduction of side effects. Alternatively, polymeric carriers can be made bioerodible in order to be eliminated by natural ways after a certain time of therapy. Core-shell fibres from coaxial spinneret or emulsion electrospinning are good candidates for the development of such devices; however difficulties remain especially in controlling the release over a sustained period. Here, we present a novel technique combining coaxial and emulsion electrospinning to produce micro-structured core-shell fibres. The design of drug microreservoirs of variable size within the bulk of the fibre combined with a tailored diffusive barrier allows modulating the release kinetics of these novel carriers. A nearly constant and linear release of the model drug Levetiracetam (M w ≈ 170 g mol -1) from PLGA emulsion-coaxial electrospun fibres is observed over 20 days. This device is aimed to be implanted into the brain for the treatment of epilepsy and is an example of the new capabilities and the promising potential that emulsion-coaxial electrospinning can provide towards the development of future drug carriers.

Keywords
sustained, weight, molecular, architectures, coaxial, low, novel, designing, soluble, drugs, highly, electrospinning, release, emulsion

Disciplines
Life Sciences | Physical Sciences and Mathematics | Social and Behavioral Sciences

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PAPER

Emulsion-coaxial electrospinning: designing novel architectures for sustained release of highly soluble low molecular weight drugs

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In drug therapy, most therapeutic drugs are of low molecular weight and could freely diffuse in the biological milieu depending on the administration route applied. The main reason for the development of polymeric drug carriers is to obtain desired effects such as sustained therapy, local and controlled release, prolonged activity and reduction of side effects. Alternatively, polymeric carriers can be made bioerodible in order to be eliminated by natural ways after a certain time of therapy. Core–shell fibres from coaxial spinneret or emulsion electrospinning are good candidates for the development of such devices; however difficulties remain especially in controlling the release over a sustained period. Here, we present a novel technique combining coaxial and emulsion electrospinning to produce micro-structured core–shell fibres. The design of drug microreservoirs of variable size within the bulk of the fibre combined with a tailored diffusive barrier allows modulating the release kinetics of these novel carriers. A nearly constant and linear release of the model drug Levetiracetam ($M_w \approx 170$ g mol^{-1}) from PLGA emulsion-coaxial electrospun fibres is observed over 20 days. This device is aimed to be implanted into the brain for the treatment of epilepsy and is an example of the new capabilities and the promising potential that emulsion-coaxial electrospinning can provide towards the development of future drug carriers.

Introduction

Among several methods for preparing bioactive loaded polymer structures for drug delivery, the electrospinning technique presents a number of advantages, in particular, the possibility to fabricate high specific surface area structures in a facile approach requiring mild preparation.[1] Electrospun fibres have been successfully developed for the encapsulation and the delivery of bioactive compounds within the body for therapeutic treatments.[2–20] Whatever the route of delivery, the polymeric device is usually required to release the drug with zero-order kinetics.[21] In the quest to produce a delivery device which has appropriate kinetics, a number of strategies have been developed including controlled erosion of the surface of the polymeric carrier loaded with a drug.[4,10,22,23] In these devices the rate of erosion has to be faster than the rate of drug diffusion, and the penetration of a solvent front into the polymer should be constant.[15,24–26] Zero order kinetics implies a homogeneous drug distribution and a release profile governed by the wetting properties of the material. Nevertheless, some issues remain, especially concerning the encapsulation of highly hydrophilic and neutrally charged drugs of low molecular weight.[12,27–29] The interaction of these types of molecules with the polymer is usually very poor and their rate of diffusion is often faster than the rate of polymer erosion. This fast rate of diffusion has detrimental effects on drug release from electrospun polymer structures. Typically drug enrichment at the surface of electrospun fibres occurs when the drug is blended into a polymer solution prior to electrospinning, and results in a severe burst release phenomenon.[30] This burst release reduces the effective lifetime of the delivery device.

Finding ways to regulate encapsulation efficiency and thus release profiles would greatly add to the inventory of strategies available for designing sustained delivery systems. A simple approach is to create a membrane-reservoir device in which an excess of the drug is surrounded by a rate-controlling membrane. Significant interest towards the fabrication of core–shell fibrous structures for biomedical applications has led to the development of coaxial electrospinning.[3,31] A coaxial dual-capillary spinneret, whereby a capillary is surrounded by a larger one (Fig. 1A), has been employed in electrospinning to fabricate core–sheath structures providing a more effective method of encapsulation for bioactive additives and hence providing a suitable drug

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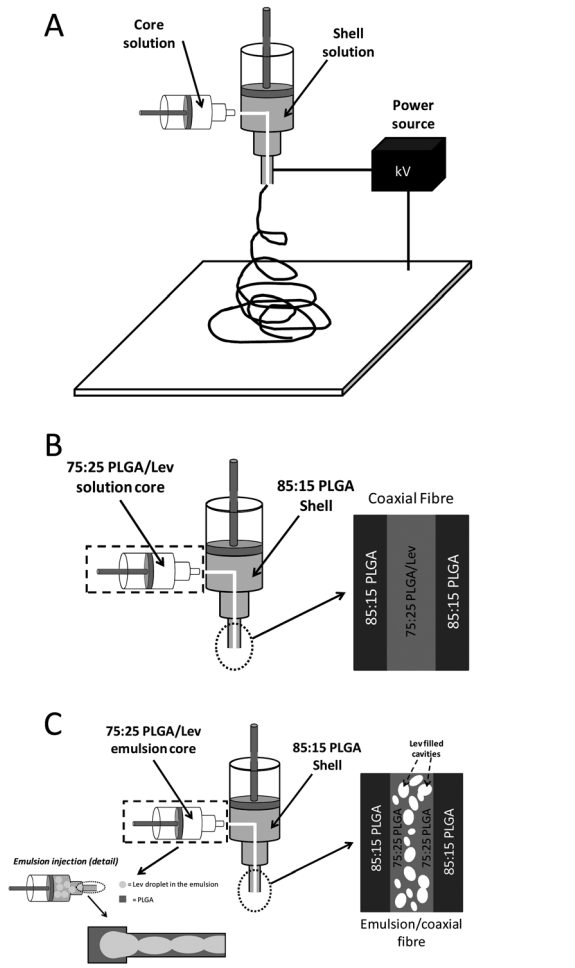

Fig. 1 Schematic drawing of the electrospinning setup (A) in the coaxial (B) and coaxial/emulsion (C) configuration showing schematics of the corresponding fibre structures produced from each method.

distribution in the polymeric fibres.[2,14] The polymer shell provides a diffuse barrier minimizing the surface enrichment. At the same time, water-soluble bioactive agents in droplets could be electrospun within hydrophobic polymers by electrospinning of water-in-oil (W/O) emulsions, namely emulsion electrospinning.[32–36] Emulsion electrospinning is similar to normal solution electrospinning, except that the solution is replaced by an emulsion. During electrospinning, the aqueous drops are stretched into elliptical shapes in the axial direction of fibres and give rise to a continuous core. The organic solvent evaporates faster than the water phase and its viscosity increases more rapidly leading to solidification and the formation of a core–shell structure.

With the continual development of new pharmaceutical drugs the delivery technologies have to face many physical–chemical issues concerning the design of suitable carriers. And when considering low molecular weight molecules presenting a high affinity for many solvents, emulsion or coaxial electrospinning may not be versatile enough to assure a reasonable encapsulation of the drug inside a local delivery system.

In this paper we present a protocol that enables drug encapsulation in order to modulate the release of a low molecular weight (170.2 g mol^{-1}) antiepileptic drug, Levetiracetam (Lev) from a microfibre structure. We employed coaxial electrospinning using an emulsion in the core as a novel way to facilitate microstructuring of fibres and the formation of drug reservoirs. The combination of the emulsion electrospinning with the coaxial electrospinning techniques provides a solution to integrate a low molecular weight, highly soluble drug into microfibre mats. Droplets containing Lev are emulsified in a drug-free polymer solution which is then coaxially electrospun with another polymer solution free of drug. Microstructured-core fibres are obtained from emulsion/coaxial electrospinning while solid-core microfiber structures resulted from coaxial electrospinning technique. The design of drug micro-reservoirs of variable size within the bulk of the fibre combined with a tailored diffusive barrier allows modulation of the release kinetics of these novel carriers.

Experimental

Materials

Poly(D,L-lactic-*co*-glycolic acid) (PLGA) ($M_w \approx 60\,000$ Da) with varying molar co-ratios was purchased from Purac (Singapore) and used as received. 75 : 25 PLGA identifies the copolymer whose composition is 75% lactic acid and 25% glycolic acid, and 85 : 15 PLGA identifies the copolymer whose composition is 85% lactic acid and 15% glycolic acid. Dichloromethane (DCM) and dimethylformamide (DMF) of analytical grade were obtained from ChemSupply PTY Ltd. Acetonitrile (ACN) of HPLC grade was purchased from Honeywell. Artificial cerebrospinal fluid (aCSF, pH 6.8) was prepared by mixing the appropriate amount of salts in Milli-Q water (18 MΩ cm^{-1}) and used as medium for the *in vitro* study. The antiepileptic drug Levetiracetam (Lev) was a gift from UCB Pharma (USA). The solubility of Lev in water is 1.04 g mL^{-1} and in DCM is 0.22 g mL^{-1}.

Reverse emulsion for electrospinning

A 17% (w/v) Lev solution in water (Milli-Q) was emulsified by vortexing in a 14% (w/v) PLGA (75 : 25) solution prepared in DCM. The aqueous phase containing Lev is the dispersed phase whereas the PLGA solution (oil phase) constitutes the continuous phase. Different dispersed-to-continuous phase volume ratios (1/55 and 1/5) were used. The reverse emulsion was stabilised with Tween 20 (0.25% w/v) and used as a core solution for electrospinning.

Fabrication of emulsion/coaxial electrospun fibres

The coaxial electrospinning set-up used in this study involved a tailor-made spinneret schematically shown in Fig. 1. The outer fluid (sheath) was a solution of 85 : 15 or 75 : 25 PLGA (20% w/v) in DCM : DMF (70 : 30). A reverse emulsion in which the drug is dissolved in water and emulsified in the polymer solution as described above was electrospun coaxially as the core. The feed rates were 2.0 mL h^{-1} and 1.0 mL h^{-1} for the core and sheath solution, respectively. Fibres were collected on a rotating disc collector. The needle tip–collector distance was maintained at 15 cm, and the spinning voltage was 24 kV. These fibres will be referred to as "emulsion/coaxial" fibres.

Fabrication of coaxial electrospun fibres

To compare with the drug blended in the core solution instead of being emulsified in an aqueous dispersed phase, 10 mg of Lev was dissolved in a 14% (w/v) 75 : 25 PLGA solution prepared in DCM constituting the inner solution. The outer fluid (sheath) was a solution of 85 : 15 PLGA or 75 : 25 PLGA (20% w/v) in DCM : DMF (70 : 30). Fibres were electrospun keeping the same conditions described previously. These fibres will be referred to as "coaxial" fibres.

In the case of the emulsion/coaxial electrospinning technique the drug is no longer blended in a polymer solution rather than dispersed in the aqueous phase which is then emulsified in a polymer solution to be used as a core.

Morphology

Morphological analysis was performed using a scanning electron microscope (SEM) (Jeol SEM) and an optical microscope (Leica DMEP). Samples at different times of incubation ($t = 0$, 1, 5 and 20 days) were visualized in order to collect information concerning the degradation of fibres. Cryo-fracturing was performed in liquid nitrogen in order to visualize the cross-section of the fibres. SEM samples were sputter-coated with a thin layer of platinum to eliminate sample charging. The diameters of the fibres were estimated from SEM images. Average pore diameters were determined by measuring the pore size for each emulsion ratio, namely 1/5 and 1/55, in the appropriate SEM images.

Swelling behaviour and contact angle

The swelling behaviour and mass loss were evaluated by incubating electrospun fibres of known weight (w_i) and geometrical surface area (a_i) in aCSF (pH 6.8) in a shaking bath at 37 °C. At different time points, samples were removed from the incubation milieu, blotted carefully with a paper and the wet surface area (a_w) was measured. The geometrical surface area of each sample was deducted from median width and length measured with a ruler. Samples were then dried for two days under vacuum and their dry weights (w_d) measured. The percentage size swelling ratio (S_a) and mass loss were calculated as follows:

$$\%S_a = \frac{(a_w - a_i)}{a_i} \times 100$$

$$\%\ \text{mass loss} = \frac{(w_d - w_i)}{w_i} \times 100$$

All experiments were performed in duplicate and the values averaged.

Contact angle measurements were obtained using a Data physics contact angle goniometer (contact angle system OCA). The data were obtained by averaging at least seven separate measurements.

Drug loading and *in vitro* release study

Experimental loading efficiency of Lev per unit weight of fibres was measured by a previously published extraction method.[37] A certain amount of material was dissolved in DCM (1 mL). Milli-Q water (10 mL) was added, vortexed for 2 minutes and left for clarification overnight. Samples from the water phase were collected and Lev concentration was quantified by high-performance liquid chromatography (HPLC, Shimadzu). Lev was detected at 205 nm (Shimadzu SPD 20A UV-Vis detector). The mobile phase, ACN (7% v/v) in purified water, was used at a flow rate of 1.2 mL min^{-1} in an Atlantis T3 reversed-phase C18 column. The injected volume of each sample was 10 μL and the retention time was 11 min. Prior to each measure, a calibration curve was prepared using 5, 10, 20 and 40 μL mL^{-1} Lev in aCSF calibrants and a correlation factor of 0.99 was obtained. The amount of Lev (M_{tot}) present in the sample was deducted from the calibration curve.

Drug release studies were performed on the fabricated samples in aCSF at 37 °C. Fibres of known mass and dimension (typically 1 cm × 1 cm) were incubated in triplicate into 1 mL of artificial cerebrospinal fluid (aCSF, pH 6.8) in a shaking bath at 37 °C. The release of Lev was followed over about a period of one month. At appropriate time intervals, all of the aCSF solution was removed from the incubated samples and replaced with an equal volume of fresh aCSF solution. The amount of Lev released (M_t) was determined by analysing the collected solutions by HPLC (Shimadzu, Prominence) following the procedure described above. All cumulative release data are plotted as an amount (M_t) released relative to the Lev loading (M_{tot}).

Results

As illustrated in Fig. 2, Lev presents a solubility range which covers a large portion of common solvents, therefore presenting difficulties in ensuring encapsulation. In order to successfully encapsulate Lev and obtain suitable long term delivery we employed a coaxial electrospinning using an emulsion in the core as a novel way to facilitate microstructuring of the core of microfibres and the formation of drug reservoirs. Here, we

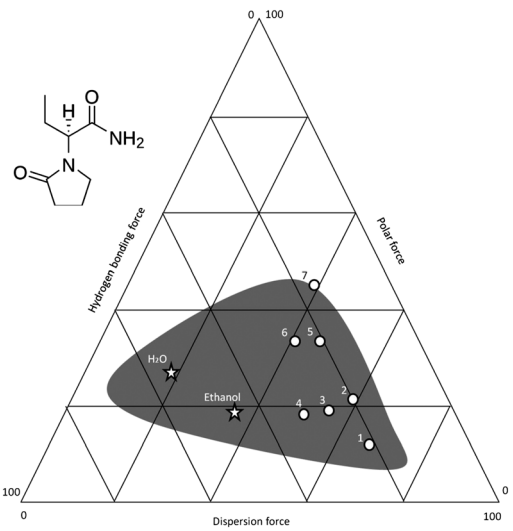

Fig. 2 The chemical structure of Levetiracetam and Teas graph representation of the solubility parameters for common PLGA solvents (1: tetrahydrofuran, 2: dichloromethane, 3: chloroform, 4: dimethylformamide, 5: ethylacetate, 6: acetonitrile, and 7: acetone). Additionally, water and ethanol are represented on the graph by an asterisk; they are PLGA non-solvent. The shaded area represents the solubility range of Lev.

present the advantage of such a combination in the design of specific drug carrier structures.

Morphology of coaxial and emulsion/coaxial fibres

The wetting behaviour of electrospun fibres with different PLGA co-ratios constituting the sheath was determined by contact angle measurements of aCSF on the surface of the electrospun structures. Both the 75 : 25 and 85 : 15 PLGA sheath fibres exhibit hydrophobic properties with contact angles of 132.6° and 145.1° respectively. In order to slow down the rate of aCSF uptake by the fibres the more hydrophobic 85 : 15 PLGA was chosen as the shell polymer whilst the 75 : 25 was chosen as the core. Furthermore, glycolic acid rich PLGA has higher affinity with Lev due to the hydrophilic–hydrophilic interaction. The enhanced affinity could prevent the drug from diffusing into the shell and thus increasing the encapsulation efficiency and loading capacity during the fabrication.

From Fig. 3A and B, it can be observed that the external morphology of emulsion/coaxial and coaxial fibres is the same. Bead-free fibres with an average diameter of 1.0 ± 0.5 μm were obtained. However, the internal structure varied between the two types of fibres. The cross-section of electrospun coaxial fibres presented a continuous core (Fig. 3C), whereas the use of an emulsion as core feeding (as described previously) allowed the formation of a unique microstructure comprising microcavities within the fibre bulk (Fig. 3D). During electrospinning, the fast evaporation of DCM allows a rapid precipitation of the polymer around individual water droplets present in the emulsion, resulting in the formation of cavities within the core. After the polymer hardens and the water evaporates, the core architecture fragments into several drug containing reservoirs. The size of the cavities is governed by the stability of the emulsion and the number of cavities is controlled *via* the dispersed-to-continuous phase volume ratio of the emulsion. Analysis of the SEMs obtained for the 1/5 and 1/55 ratio samples showed an average pore size of 0.91 ± 0.09 μm ($n = 59$) and 0.72 ± 0.06 μm ($n = 61$) respectively.

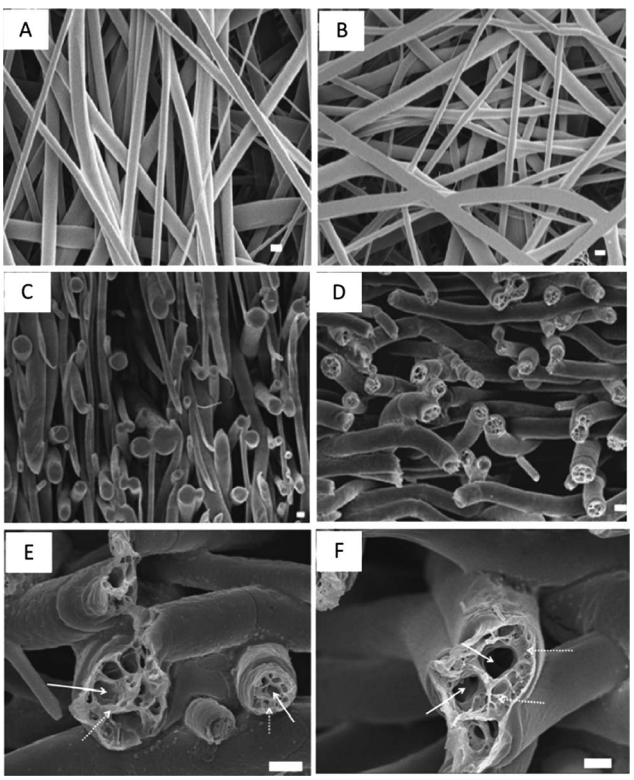

Fig. 3 Electrospun fibres consisting of PLGA 75 : 25 core and 85 : 15 sheath observed by SEM: top view (A and B) and cross-section (C, D, E and F). Coaxial fibre cores (A and C) were formed from a PLGA solution in which Lev was blended and emulsion/coaxial fibre cores (B, D, E and F) were formed from a reverse emulsion in which Lev was dispersed in the aqueous phase. The dispersed-to-continuous phase volume ratio is used to control the cavity size and diffusive length of the release system. A small ratio (1/55) (F) allows the formation of small cavities (line arrow) and a large diffusive membrane (dash arrow), whereas a bigger ratio (1/5) (E) allows larger cavities (line arrow) and shorter diffusive length (dash arrow). Scale bars are 1 μm.

The introduction of an emulsified core in the coaxial electrospinning technique leads to an extremely versatile design process for structuring the core of the fibres. Fig. 3E and F show emulsion/coaxial fibres resulting from 1/5 and 1/55 dispersed-to-continuous phase volume ratio respectively. It was observed that using a larger phase ratio of 1/5, numerous cavities were formed and the cavity wall thickness was thin (solid arrow for cavity and dashed arrow for wall in Fig. 3E), whereas a smaller phase ratio led to the formation of fewer small cavities separated by thick walls (solid arrow for cavity and dashed arrow for wall in Fig. 3F). Using a large dispersed-to-continuous phase volume ratio which involves a large aqueous phase volume leads to a large number of droplets emulsified within the polymer continuous phase, therefore, allowing the formation of numerous cavities in the core separated by thin walls. On the other hand, using a small ratio involves a small aqueous phase volume forming fewer cavities separated by thick walls after hardening. In this study, a very small phase ratio of 1/55 was chosen mainly for two reasons: first to obtain few small cavities within the core acting like small reservoirs of the drug and secondly to build thicker cavity walls in order to provide a longer distance for the drug to diffuse from the cavity reservoir to the released environment through the membrane formed by the polymeric matrix of the core and the shell of each fibre (Fig. 4).

Under physiological conditions (incubation in aCSF, pH 6.8 at 37 °C), both types of electrospun fibres showed considerable shrinkage of ~70% of the initial area after 1 day of incubation (Fig. 5A and B). This phenomenon has been previously reported.[8,38–41] After one day of incubation, it is expected that a drastic shrinkage of the amorphous poly(D,L-lactide-*co*-glycolide) fibres takes place. This occurs for the following reasons: (i) PLGA fibres have a glass transition between 44 °C and 48 °C (data not shown) close to the incubation temperature (37 °C) and (ii) both electrospun PLGA fibres are highly oriented (due to the electrospinning process) but without crystalline properties. As a result, the relaxation of extended amorphous chains under incubation conditions near the glass transition temperature causes a large dimensional change (shrinkage) without being hindered by crystalline regions.

Fig. 5C and D show SEM images recorded at different time points. No hydrolysis induced porosity or cracks induced by degradation were observed with fibres keeping a relatively

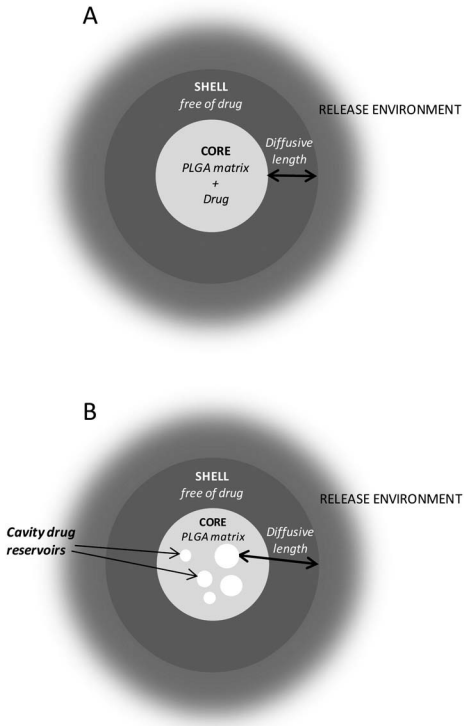

Fig. 4 Cross-section schematic representation of the diffusive length with coaxial (A) and emulsion/coaxial (B) fibre architectures.

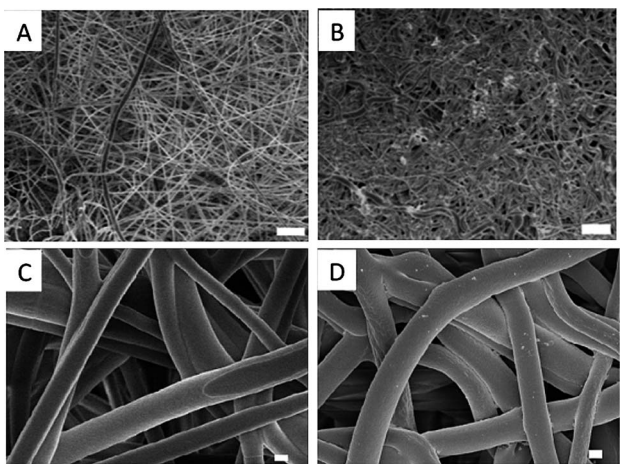

Fig. 5 Emulsion/coaxial fibres before (A and C) and after (B and D) 20 days of incubation in aCSF, pH 6.8, at 37 °C. Scale bars are 1 μm.

smooth surface over a 20 day time period. No significant mass loss was observed up to 20 days of incubation. Beyond 20 days, 2% and 9% mass loss were recorded for the coaxial or the emulsion/coaxial fibres, respectively. These observations suggest that PLGA electrospun fibre degradation is most likely to occur from the internal part (bulk) and this is in accordance with previous observations.[13] We believe that the mass loss difference between coaxial and emulsion/coaxial fibres is due to the erosion rate taking place within the different structured cores. Since the emulsion/coaxial fibre core presents a higher internal surface area, due to the presence of cavities, the erosion front formed along each cavity wall is larger. Thus, a larger amount of material eroded from the emulsion/coaxial fibres than from the coaxial fibres is expected to be observed.

Drug release

The *in vitro* release profiles of the coaxial and emulsion/coaxial fibres are shown in Fig. 6. The total Lev loading of the samples was experimentally calculated to be 2.8 ± 0.3 μg mg^{-1} for both type of microfibres. Release profiles show a variation between the coaxial and emulsion/coaxial electrospun carriers for the same drug loading. A nearly linear sustained release is obtained over 18 days for emulsion/coaxial fibres. The rate of release over time is nearly constant with some little variation and was evaluated at about 1% of the total loading amount released per day, whereas from coaxial fibres a decline in the rate of release over 4 days was observed. After 18 days, 47% of the total drug loading amount has been released from emulsion/coaxial fibres whereas from coaxial fibres the same amount has been released in less than 4 days. Halliday *et al.*[42] recently reported release of Lev from PLGA sheets and wet-spun fibres. Their results showed that PLGA flat sheets containing Lev produced a burst release of 56% of the loaded drug in the first 24 hours followed by 90% release by day 7. The wet-spun fibres also show significant burst release of 69% in 24 hours followed by 80% by day 7. The release profiles presented in Fig. 6 clearly show improved encapsulation and release from the coaxial and emulsion/coaxial electrospun fibres compared to these sheets and wet-spun fibres.

Discussion

During the first 20 days of incubation, no significant mass loss was observed from the electrospun fibres, however Lev release does occur. This suggests that the diffusion of the drug through the polymeric matrix is faster than the matrix erosion kinetics. Hence, within the time frame for this study, we considered that the release of Lev from the fibres is mainly governed by diffusion processes. The concentration gradient is the driving force for diffusion (First Fick's law) and, in such systems the driving concentration gradient is between the drug reservoir and the

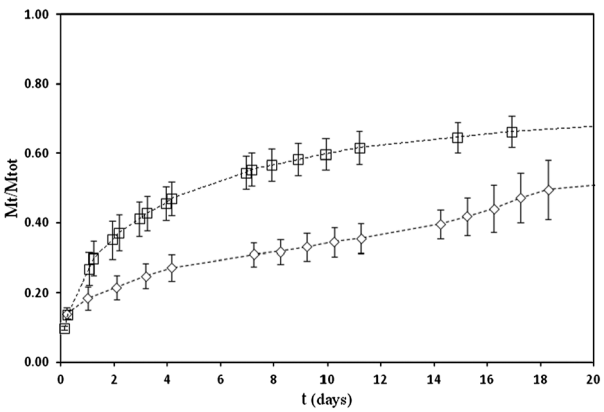

Fig. 6 Cumulative release of Lev in aCSF (37 °C, pH 6.8) from coaxial (□) and emulsion/coaxial (◇) electrospun fibres. Drug amount (M_t) released relative to drug loading (M_{tot}) of the carrier. Error bars represent standard errors from the average calculated on three specimens.

release environment. In our system Lev is located within cavities in the core of the fibres and partitioned from the release environment by the polymeric matrix which constitutes a rate controlling membrane. Lev will diffuse across the membrane to finally move into the release environment. Therefore drug distribution within a device is of primary importance in the design of a drug carrier. A near constant rate of release can be achieved if the drug reservoir remains saturated with drug and the rate of transport across the membrane is sufficiently low compared to the rate of substance clearance into the release environment.

In our study we can observe, in the first 3 hours, a relatively low burst release of drug of about 10% of the loading for both types of fibres (coaxial and emulsion/coaxial). This burst is likely due to the presence of small amounts of Lev in the shell of the fibres that diffuse from the loaded core during the fabrication process. In addition, since no prewashing of the fibres was performed prior to undertaking the release experiments this burst release could also be attributed to any surface bound drug. Following this fast release of drug, a concentration gradient is established within the device, between the drug reservoir and the release environment, and is reflected in the release profile obtained from the fibres. The release profile from the coaxial fibres presents a linear profile up to 4 days which is followed by a progressive slowdown of the release, whereas release from emulsion/coaxial fibres presents a slower and nearly constant release over 20 days. This differentiation in the release behaviour between these two types of fibres is believed to be induced by the microstructuring of the core and the Lev confinement within the core of the emulsion/coaxial fibres. In the case of coaxial fibres, the diffuse distance, between the polymeric matrix forming the core of fibres and the release environment, is smaller than for the emulsion/coaxial fibres. The diffuse length consists of the continuous polymeric matrix in the core and the shell thickness (see Fig. 4A and B). Moreover, the drug reservoir for coaxial fibres constitutes the whole core of the fibre where the drug is dispersed homogeneously, whereas emulsion/coaxial fibres provide small fragmented reservoirs located in the core. As a result, we observe in the coaxial fibre release profile a short linear part up to 4 days reflecting the concentration gradient of the drug established within the small diffusive membrane. At times longer than 8 days the rate of release appears to slow down, possibly due to a reservoir which is no longer saturated with drug. Emulsion/coaxial fibres provide a long diffuse distance and a saturated reservoir which allow the establishment of a low concentration gradient slowing down the release of drug up to at least 18 days of incubation following the formulation used in this study. A better confinement of the drug inside the cavity-like core and a large diffusive barrier are efficient enough to provide a sustained release of highly soluble low molecular weight drug for many days.

Conclusions

In summary, we have developed an extremely versatile and powerful electrospinning technique to fabricate novel drug delivery platforms. We successfully showed that by using reverse emulsion as a core feed new fibre architectures can be designed. This technique provides a microstructured core which can be used as small drug reservoirs surrounded by a diffusive barrier producing new dimensions in the design of polymeric drug carriers. A nearly linear release of small molecular weight drug over 18 days was observed whereas classical core–shell fibres in comparison provided a linear release for 4 days followed by a steady state. The internal fibre architecture can be tailored by adjusting the emulsion dispersed-to-continuous phase ratio. Finally, emulsion-coaxial electrospinning represents a new and promising approach for the design of future drug carriers.

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