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Optimizing partition-controlled drug release from electrospun core–shell fibers

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ABSTRACT

Controlled release of hydrophilic entities, such as peptides, proteins and even pDNA, is difficult to accomplish with conventional approaches. This work suggests one possible approach for controlled release of such actives using electrospun core–shell fiber structures. In particular, we propose strategies for partition control of the release. The fibers consist of two layers, with the outer polymer sleeve serving containing the inner core, in which the drug is encapsulated. By varying the physical and chemical properties of the core and shell solutions, we have shown that the release rate of a hydrophilic drug, metoclopramide hydrochloride, is controllable. Experimental results show a clear difference in the release pattern between monolithic fibers made of hydrophilic and hydrophobic polymers and various core–shell fibers with PCL, PLLA and PLGA 80/20 as shell polymers. The study yields insight into when partition control of release can be achieved in core–shell fibers, and with that, options for controlled release systems for hydrophilic drugs, peptides and pDNA.

1. Introduction

As drug carriers, biodegradable polymers have found extensive use. Commercially, there have been a few systems based on biodegradable carriers, including Lupron-Depot®, the now-discontinued Nutropin® depot, as well as Glia-del®, which is an implanted wafer. As we understand more and more about the properties of biodegradable polymers, their use continues to expand.

Various dosage forms have been fabricated using biodegradable polymers in order to achieve controlled drug release. These include microspheres (Huang et al., 1999), films, millirods (Qian et al., 2001), nanoparticles (Jeong et al., 2004). These drug delivery vectors have been studied widely for their drug release profiles and all of them have some limitations. Limited drug capacity and the "burst release" effect are two common problems. Attempts to overcome the burst have been made, with varying degrees of success. For example, Huang et al. (1999) coated microspheres of drug-carrying block PLA/PEG with gelatin; however, there were some concerns regarding the interference of gelatin with drug release.

Core–shell structures are one of the several approaches made to obtain a controlled release profile, potentially yielding a zero-order profile. He et al. (2006) prepared a reservoir-type drug release device by encapsulating tetracycline hydrochloride (TCH) in the PLLA ultrafine fibers prepared by altering the polymer concentrations in the shell solution. Control was achieved over the release of the core drug, although the explanation that the drug is released only through PLLA degradation was not substantiated nor does it appear reasonable, given the fairly slow degradation rates for PLLA. Another approach of preparing core–shell structures has been made by loading the shell with the drug. Zilberman (2007) have prepared such structures by coating the PLLA fibers and nylon sutures with protein-loaded PDLGA. The idea was to retain the mechanical strength of the fiber while achieving sufficient control over the protein (horse radish peroxidase, HRP) elution. However, the protein (HRP) was loaded in the shell rather than the core; hence most of the protein was released in a burst as expected, due to the relatively hydrophilic character of the eluent.

In this work, we evaluate the usefulness of core–shell fibers made by electrospinning (Sun et al., 2003; Dror et al., 2007), with a view to minimize effects such as the burst release. Electrospinning provides a simple and versatile method for generating ultrathin fibers from a variety of materials including polymers (Li and Xia, 2004). Polymeric nanofibers have proved to be attractive materials for a wide range of applications because of their unique properties, especially very high surface area to volume ratio, flexibility in surface functionalities, superior mechanical properties, similar structural morphology to the fibrillar ECM (extracellular matrix), etc. (Boland et al., 2001; Li and Xia, 2004; Li et al., 2005, 2006). However, many of the ultrathin polymeric fibers have failed to control the release of drug because of incompatibility between the polymer and the loaded drug (Kenawy et al., 2002, 2007; Kim et al., 2004; Jing et al., 2005).

Control of release of hydrophilic bioactives from biodegradable polymer matrices has always presented a challenge. In general,

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there is a considerable amount of initial burst release, caused mainly by inadequate solubility of the bioactive in the polymer carrier. If on the other hand, a hydrophilic polymer is used as the matrix, the polymer swells in aqueous media, accelerating the release. We were interested in controlling the release of a hydrophilic drug, and understanding the factors that control the burst effect as well as the rate of subsequent release. We studied a core–shell fiber system, fabricated by co-electrospinning, for drug delivery. In this system, the drug was loaded in the core which was surrounded by different shells of various polymers. We asked the question: under what conditions can true partition control be achieved in such a system and how it affects the drug release pattern? Comparison was made with release from monolithic fibers in order to evaluate the efficacy of partitioning in the core–shell systems.

2. Materials and methods

2.1. Materials

PLLA (poly-L-lactide) (Mw = 152 kDa), PCL (poly ε-caprolactone) (Mw = 80 kDa) and PLGA80/20 (Mw = 120 kDa) were obtained from Purac Far East Pte., Singapore. PLGA 80/20 is a copolymer with lactide and glycolide residues in 80:20 ratio. In this study, this copolymer will be referred as PLGA for the sake of simplicity as we have used only one type of PLGA. PVA (polyvinyl alcohol) (99+% hydrolyzed; Mw = 124–186 kDa) was purchased from Aldrich Chemical, Milwaukee, WI, USA. Metoclopramide hydrochloride (referred to as MS, or metoclopramide salt), a dopamine receptor antagonist with antiemetic and prokinetic properties, was used as a model drug for this study. It was purchased from Sigma–Aldrich. Phosphate buffer saline (pH 7.4) and Rose Bengal were purchased from Sigma–Aldrich. Chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2, stabilized with 100–150 ppm amylene) and acetonitrile (CH_3CN) were purchased from TEDIA. Dimethylformamide (N,N-dimethylformamide; C_3H_7NO) was purchased from MERCK. Triton® X-100 was purchased from Sigma–Aldrich.

2.2. Electrospinning of fibers

Electrospinning was performed to prepare monolithic (fibers spun with single polymer solution) and core–shell fibers using the parameters tabulated in Table 1. These parameters, guaranteeing a stable electrospinning process, were reached after series standardizations with respect to polymer concentrations, flow rates and applied voltage.

A combination of chloroform and DMF (N,N-dimethylformamide) was used as the organic solvent to dissolve the hydrophobic polymers (PCL, PLLA and PLGA). DMF was added to chloroform in order to increase the electrical conductivity (Tan et al., 2005) and vapor pressure of the solvent. Increase in conductivity adds to the spinnability of the solution whereas increase in vapor pressure of the solvent helps prevent blockage at the needle tip by delaying the otherwise premature drying of the polymer solution (Theron et al., 2004). PVA (polyvinyl alcohol), which is a hydrophilic polymer, was dissolved in water as mentioned in Table 1. For, monolithic PVA fibers, 0.5% (v/w of PVA) Triton® X-100 (a surfactant) was added to the PVA solution to reduce the surface tension of the solution which was not spinnable otherwise. However, this problem of spinnability was not encountered in co-electrospinning due to the interfacial properties between the shell and the core solutions (Reznik et al., 2006).

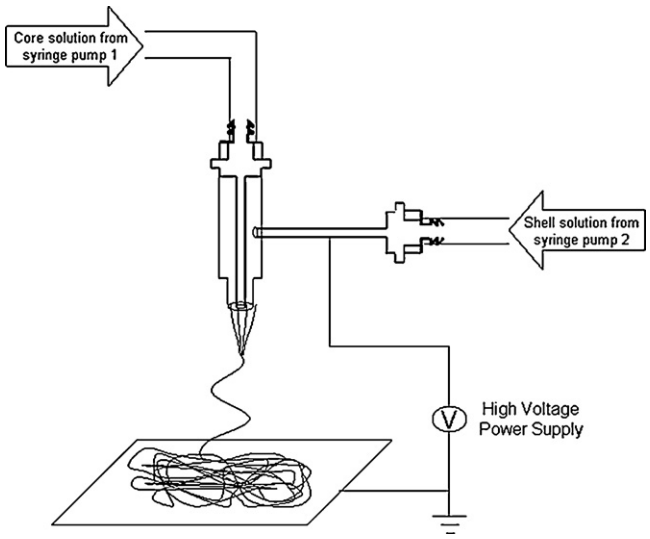

Fig. 1. Schematic diagram of core–shell electrospinning.

For electrospinning of the fibers, polymer solutions, extruded through a small needle at rates controlled by syringe pump, were subjected to high electric field. At the high electric field, the polymer solution, by virtue of electrostatic repulsion, underwent extensive stretching to yield ultrafine fibers.

In the case of electrospinning of monolithic fibers, the spinneret supplied only one solution, through a needle, assisted by a syringe pump (PHD2000 infusion, Harvard Apparatus). A special arrangement was made for the core–shell spinning process which involved a tailor-made spinneret (Dror et al., 2007) which could supply the shell solution around the core needle (Fig. 1). Feeding of both solutions to the spinneret was assisted by two syringe pumps (PHD2000 infusion, Harvard Apparatus and Infutec 610/A, Medical Systems Ltd.) operating independently for core and shell

Table 1
Details of metoclopramide loaded fiber samples.

Samples	Core		Shell		Accelerating voltage (kV)
	Composition	Flow rate (ml/h)	Composition	Flow rate (ml/h)	
PCL monolithic	9% PCL in chloroform + DMF (80:20) + 1% (w/w of PCL) MS	1.5	N/A	N/A	25
PLLA monolithic	6% PLLA in chloroform + DMF (80:20) + 1% (w/w of PLLA) MS	1.0	N/A	N/A	23
PLGA monolithic	12.5% PLGA in chloroform + DMF (80:20) + 1% (w/w of PLGA) MS	1.0	N/A	N/A	24
PVA monolithic	8% PVA in water + 0.5% (v/w of PVA) Triton® X-100 + 1% (w/w of PVA) MS	1.0	N/A	N/A	16
PVA–PCL core–shell	8% PVA in water + 1% (w/w of PVA) MS	0.5	10% PCL in chloroform + DMF (80:20)	4.0	26
PVA–PLLA core–shell	8% PVA in water + 1% (w/w of PVA) MS	0.5	6% PLLA in chloroform + DMF (80:20)	4.0	22
PVA–PLGA core–shell	8% PVA in water + 1% (w/w of PVA) MS	0.5	12.5% PLGA in chloroform + DMF (80:20)	4.0	23

solution, respectively. The temperature and relative humidity (R.H.) remained in the range of 24–25 °C and 44–50%, respectively, during the course of electrospinning. Solution and processing parameters such as solvent type, concentration of monolithic, core and shell solutions (wherever applicable), flow rates and applied voltage, are presented in Table 1.

The fibers were collected on a vertically rotating disc collector using the setup described by Theron et al. (2001). The distance between the needle tip and the collector was maintained at 15 cm. The electrospun fiber mat was dried in a vacuum chamber for 3 days to achieve evaporation of most of the solvents from the fibers. The fibers mats were then stored by sealing in polythene bags and subsequently used for further analyses.

It is important to note that, in the case of core–shell fibers, the overall drug loading is lower than the monolithic fibers as the shell polymer does not contain any drug at the time of electrospinning.

2.3. Morphological characterization of the fibers

Morphology of the fibers was characterized by scanning electron microscopy (SEM, JEOL JSM 6360A) following Au coating of the fiber mats. For cross-sectional views, the oriented fiber mats were cut in liquid nitrogen using guillotine technique (Dror et al., 2007).

2.4. Preparation of fluorescent dye loaded fibers

In order to observe the distribution in the core–shell fibers, fluorescent dye loaded fibers were prepared. Rose Bengal was chosen as the fluorescent dye because of its hydrophilic nature (high water solubility ~360 mg/ml), comparable to the hydrophilicity of metoclopramide salt (water solubility >50 mg/ml).

In this process, MS and Rose Bengal (RB) were mixed in water overnight, keeping the MS:RB ratio as 99:1. The solution was then added to the PVA solution to get 1% (w/w of PVA) loading of (MS + RB). The core–shell fibers were then prepared on glass slides for very short durations (5–10 s) using the parameters mentioned in Table 1. The fibers so obtained were dried overnight in dark condition in a vacuum chamber to achieve evaporation of most of the solvents from the fibers, and then quickly analyzed by confocal microscopy.

2.5. Confocal microscopy

The fluorescent dye loaded fibers were observed in confocal fluorescence microscope (Leica TCS SP5). The fluorescence dye (Rose Bengal) had excitation wavelength at 525 nm and maximum emission wavelength at 575–600 nm.

2.6. ATR-FTIR spectroscopy

In order to testify the coverage of the core by the shell, ATR-FTIR (Attenuated Total Reflectance-Fourier Transformed Infra Red) spectroscopy (Perkin Elmer Spectrum GX Shelton, CT, USA) of the core–shell fibers was performed. The collected spectra, in the range of 600–4000 cm^{-1}, were compared with the monolithic PVA fiber loaded with MS and monolithic fibers of the shell polymers without MS loading. ATR-FTIR is a surface characterization technique which involves total attenuated reflection of the infrared beam when the beam enters the sample surface.

2.7. Release study

The pieces of fiber mats were cut, weighed and incubated in 5 ml of phosphate buffer saline (PBS) (pH 7.4) in 10 ml bottle with which were then tightly capped and placed inside the incubator maintained at 37 ± 0.1 °C in order to study the release profile of the metoclopramide salt or MS. At specific intervals, the 2 ml of the medium was withdrawn and replaced with fresh buffer in order to maintain the sink conditions. The time interval was determined keeping in mind the balance between release of detectable amount of drug into the medium and maintenance of the sink condition, which essentially means that the volume of the medium should be at least 10 times higher than the minimum volume needed to achieve the solubility limit of the drug in the medium. The drug release was quantified by UV Spectrophotometry (UV Pharmaspec 1700 UV–vis Spectrophotometer, Shimadzu, Kyoto, Japan), at 273 nm, using a standard curve, prepared by using MS solutions of known concentrations in phosphate buffer saline (pH 7.4).

2.8. Drug loading

In order to quantify the drug loading, weighed pieces of the fiber mats were dissolved in 5 ml of dichloromethane. The resulting solutions were then quantified by UV Spectrophotometry at 273 nm with the help of a standard curve drawn with known concentrations of MS solutions in dichloromethane. The same procedure was followed for quantification of residual drug in the films recovered after the release experiment. PVA monolithic fibers were dissolved directly in 5 ml of water at 60 °C. In the case of core–shell fibers containing PVA (which is insoluble in dichloromethane), dichloromethane led to dissolution of the shell polymer, which was then removed from the bottle to leave the undissolved PVA core. The remaining PVA core was then dried and dissolved in 5 ml of water at 60 °C. Concentration in the aqueous solution was calculated using standard curve drawn with known concentrations of MS solutions in water. The total MS loading in the core–shell fibers, with PVA as core, was calculated by adding the MS concentration in dichloromethane and aqueous solutions.

All the experiments were performed in triplicates and the results are presented as mean ± standard deviations.

3. Results and discussion

3.1. Electrospinning of fibers

Core–shell and monolithic fibers were electrospun successfully. Fig. 2 represents the SEM images of the monolithic fibers. The PCL fiber sample seems to have many particles deposited on its surface (Fig. 2b; arrows) which we suspect to be undissolved drug particles. This, however, is not the case with the PVA, PLGA and PLLA monolithic fibers. The presence of these undissolved drug particles can lead to a high burst of drug release initially. We infer with this observation that PCL has significantly lower MS solubility.

The core–shell fibers, however, do not show any drug particles on their surface (Fig. 3) which is expected as there is a shell (without drug) surrounding the drug loaded polymer core.

3.2. Confocal microscopy

In order to look in more detail at the distribution of drug in these fibers and to verify the core–shell structure, confocal microscopy was performed within 24 h of fiber preparation. It was of special interest to compare the location of MS drug (or drug associated with the tag, Rose Bengal or RB) in the core–shell fibers. As apparent from the confocal images (presented here as overlay of fluorescent and bright field images) of core–shell fibers (Fig. 4), the fluorescent dye appears to be restricted within the core which is clearly distinguishable from the shell. This demonstrates the core–shell structure as the dye, added only to the core polymer (PVA) solution, is expected to stay within the hydrophilic core after electrospinning, at least for the period of this observation.

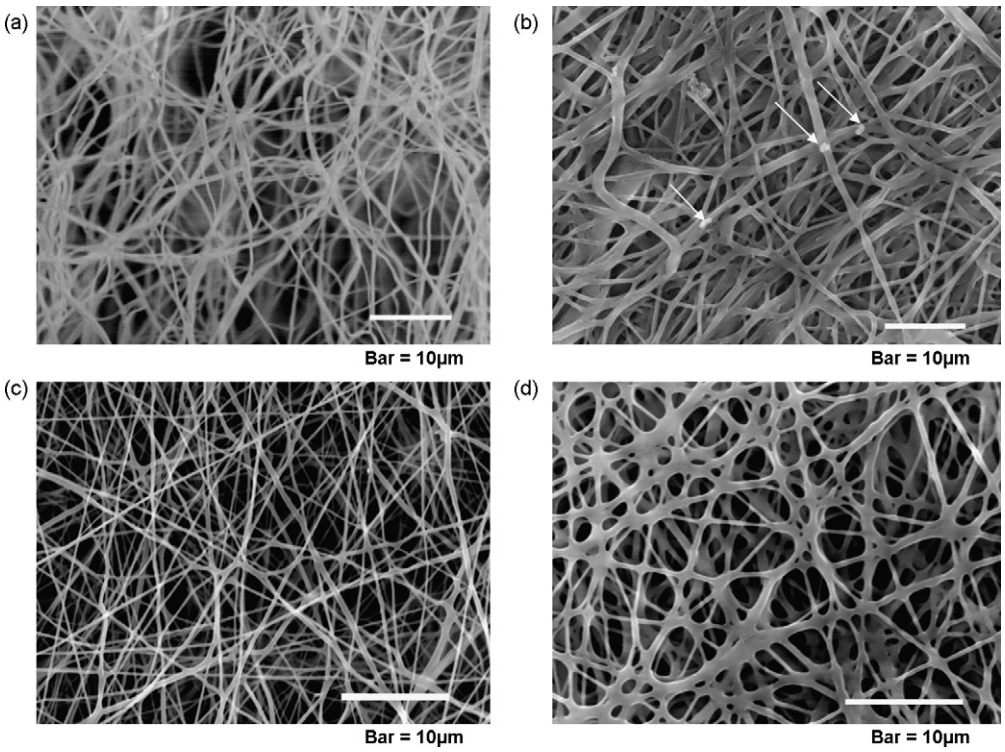

Fig. 2. SEM images of electrospun monolithic fibers loaded with metoclopramide salt: (a)PVA, (b)PCL, (c) PLLA, and (d) PLGA.

3.3. ATR-FTIR spectroscopy

The ATR-FTIR spectra of the PVA–PCL (Fig. 5e), PVA–PLLA (Fig. 5f) and PVA–PLGA (Fig. 5g) show that the core–shell fibers resembled the monolithic fibers of the shell polymers without loaded drug, i.e. PCL monolithic (Fig. 5a), PLLA monolithic (Fig. 5b) and PLGA monolithic (Fig. 5c), respectively. The exclusive broad peak at 3200–3600 cm^{-1}, which is representative of–OH, in the spectra of PVA monolithic fibers (Fig. 5) is masked in all the core–shell fibers (box in Fig. 5). This indicates the absence of PVA on the surface of

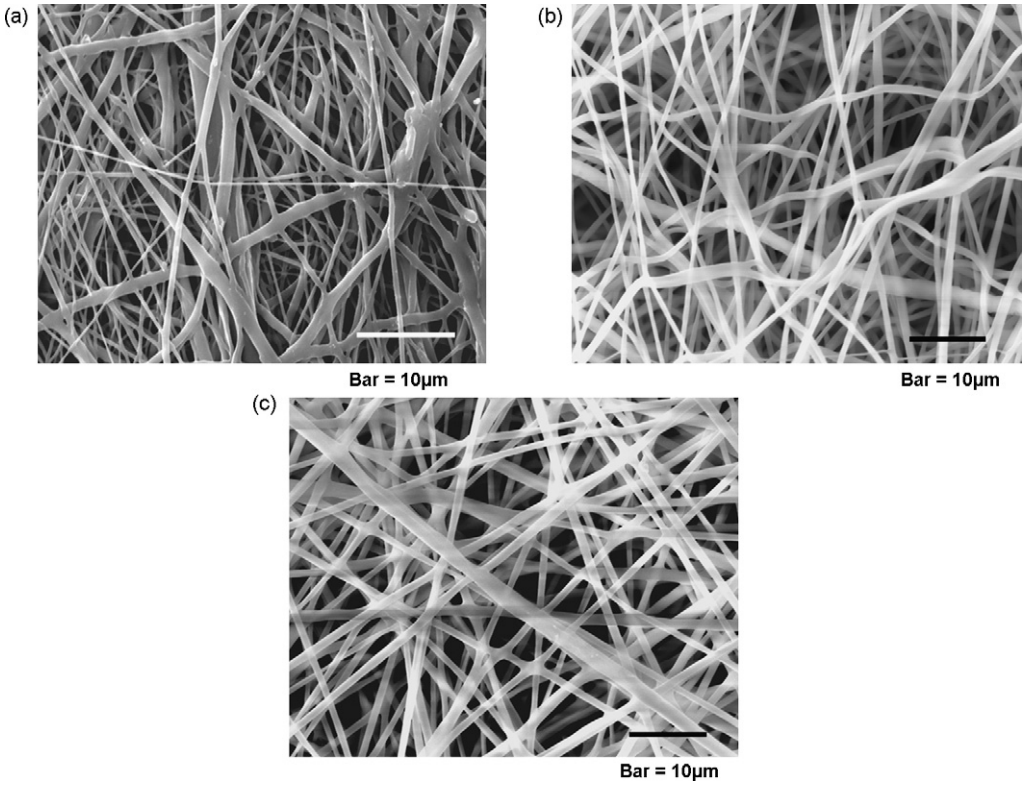

Fig. 3. SEM images of electrospun core–shell fibers: (a) PVA–PCL, (b) PVA–PLLA, and (c) PVA–PLGA.

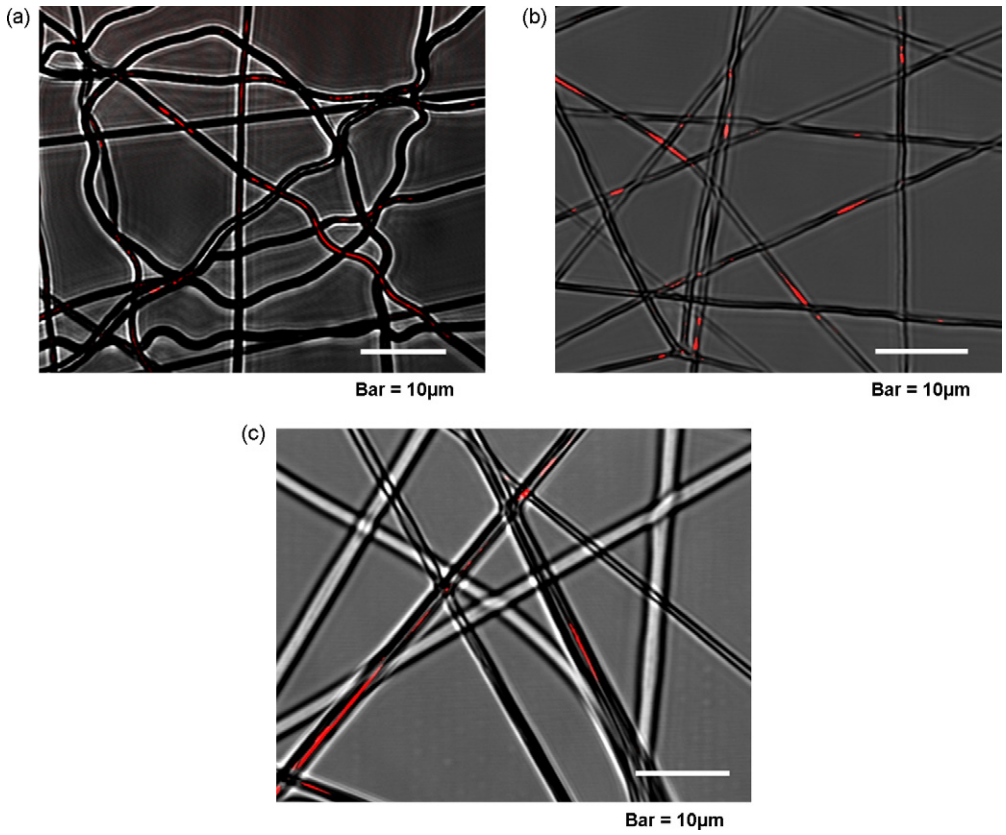

Fig. 4. Confocal images of core–shell fibers with Rose Bengal added in core (PVA) solution: (a) PVA–PCL, (b) PVA–PLLA, and (c) PVA–PLGA.

these fibers, at least up to a depth of 0.5 μm, which is the ATR depth of penetration. It must be noted that the ATR-FTIR cannot pick up the effects of porosity, unless the pore formation somehow exposes the core at the depth of penetration of the IR.

3.4. Drug release study

When we compare the MS release profiles from PVA, PCL and PLGA monolithic fibers (Fig. 6), we find that all monoliths exhibit a certain amount of burst release (amount of drug released at 6 h), and that the extent of burst decreases in the following order:

PVA > PCL > PLGA 80/20 > PLLA

The explanation is as follows. The PVA monolith swells immediately upon contact with buffer, releasing most of the drug as a burst (more than 90%), exhibiting no control over the drug release, as expected from a hydrophilic carrier. The PCL has undissolved drug on the surface (Fig. 2b) which releases in the first 6 h as a burst.

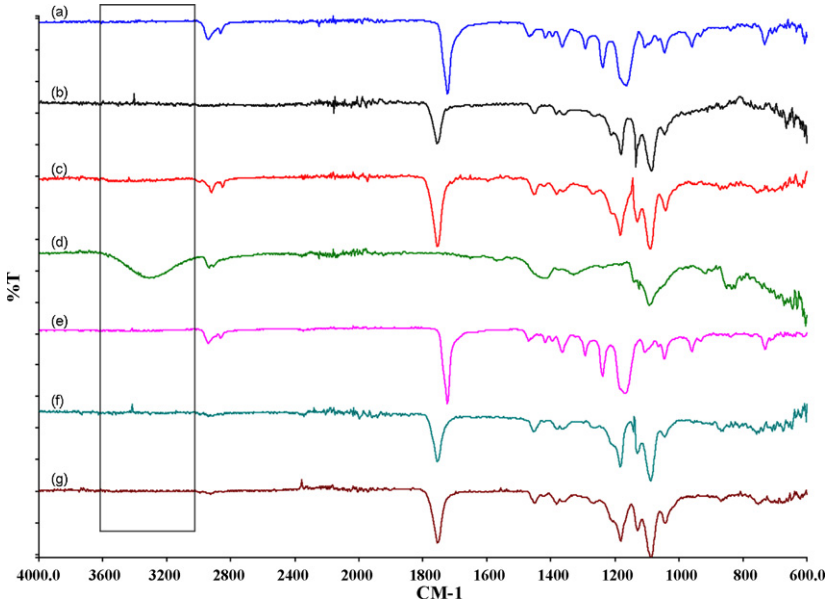

Fig. 5. ATR-FTIR spectra of monolithic fibers for shell coverage: (a) PCL monolithic, (b) PLLA monolithic, (c) PLGA monolithic, (d) PVA monolithic fibers, (e) PVA–PCL core–shell, (f) PVA–PLLA core–shell, and (g) PVA–PLGA core–shell fibers.

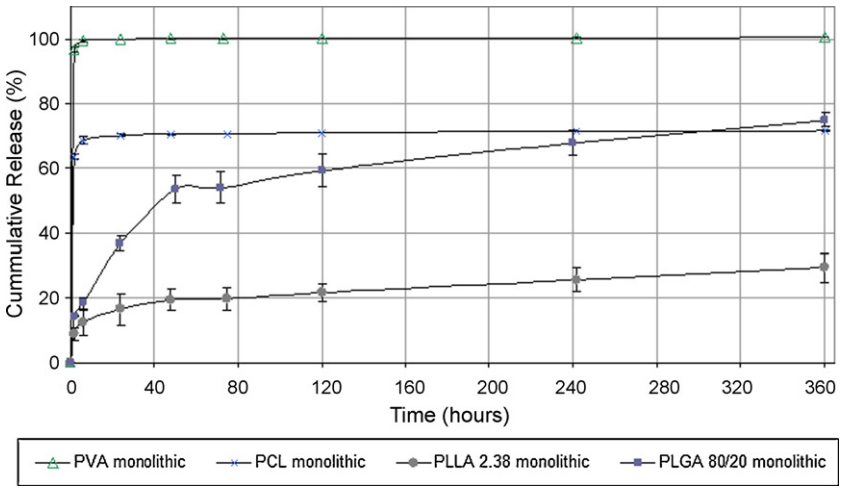

Fig. 6. Release profile of metoclopramide salt from PVA, PCL, PLLA and PLGA monolithic fibers.

Similarly, PLGA has undissolved drug particles as well, although these are not seen in the SEM as particles, probably due to their smaller amount. Although we expected PLLA also to have undissolved drug, it is likely that the higher T_g of the PLLA (60–65 °C) effectively trapped most of the undissolved drug inside the bulk of the fiber than on its surface, so that only the 10% or so on the surface releases out quickly. For PCL, which has a very low T_g (−60 °C), such trapping is not possible, and all undissolved drug migrates to its surface quickly after fiber preparation, and is released as a burst.

The release profiles of MS from PCL monolithic and PVA–PCL fibers are shown in Fig. 7. It can be observed that PCL monolithic fibers have undergone a 'burst release' of about 70% of its drug content within a few hours of incubation in PBS. Locating the drug in a hydrophilic core of PVA has lowered this burst to about 55%, clearly showing that the amount of undissolved drug has been reduced by the use of this core polymer. But, the suppression by the shell is not sufficient to be termed as controlled release. This is most likely due to the presence of pores (either micron or nano-sized) in the PCL shell, which is not unexpected based on the concentration and molecular weight of PCL used here. Enhanced release profile from a fiber with PCL shell has been reported and such effect was attributed to water sorption in the nanopores of PCL which in turn facilitates 'desorption' from the surface of the core polymer, the rate-limiting step of the release mechanism from the fibers (Srikar et al., 2008). We believe that these pores in the PCL shell allow easy access of the release medium to the swellable core polymer, facilitating rapid release of drug.

To confirm whether the nanoporosity of the PCL shell has an effect on the drug release from this system, an experiment was performed whereby the conditions for a greater degree of nanoporosity in the PCL shell were intentionally created. This was done by lowering the concentration of the PCL solution from 10 to 7% (other spinning conditions were altered slightly to get stable spinning). Using a lower concentration of the polymer solution in a volatile solvent generally results in higher porosity (Casper et al., 2004). Release from these PVA–PCL fibers (Fig. 8) does show an enhanced burst effect, attesting to the increased access of water to the PVA core through the pores.

On comparing MS release from PLLA monolithic and PVA–PLLA core–shell fibers (Fig. 9), there is very little difference in release profiles. This is because:

(a) the PLLA shell is not porous and
(b) diffusion through the glassy PLLA is the rate-limiting step, not the partitioning from PVA into PLLA.

For PLGA monolithic and PVA–PLGA core–shell fibers the suppression of drug release is more pronounced (Fig. 10) as there is significant burst from the monolithic fiber and very slow release from the core–shell fibers. This is where the partitioning effect is

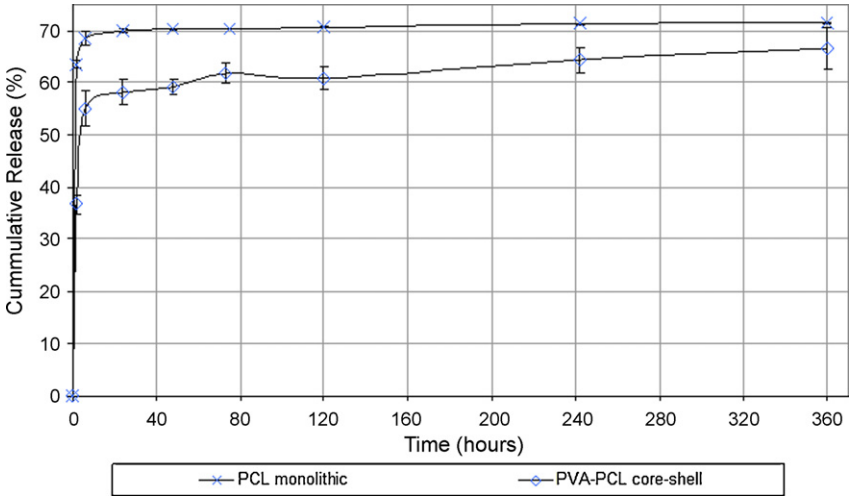

Fig. 7. Release profile of metoclopramide salt from PCL monolithic (electrospun from single solution) and PVA–PCL core–shell fibers.

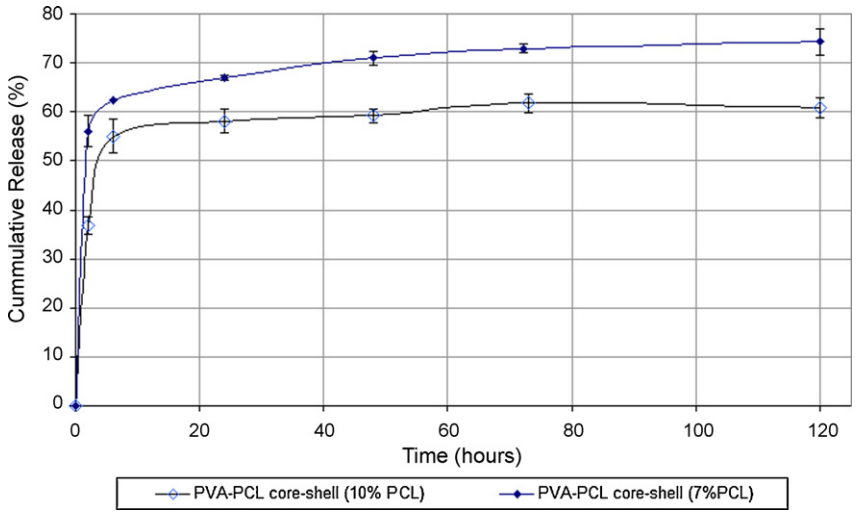

Fig. 8. Comparison of release of MS from two PVA–PCL fibers, with differing concentrations of the shell (PCL) solution.

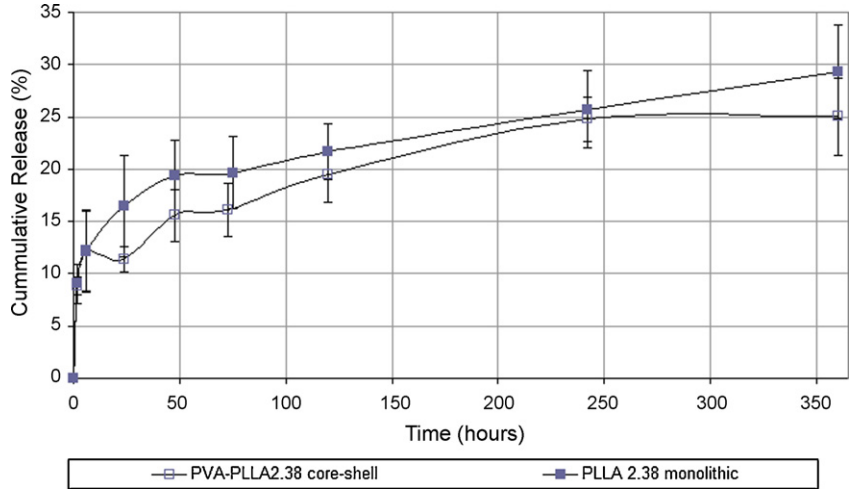

Fig. 9. Release profile of metoclopramide salt from PLLA monolithic and PVA–PLLA core–shell fibers.

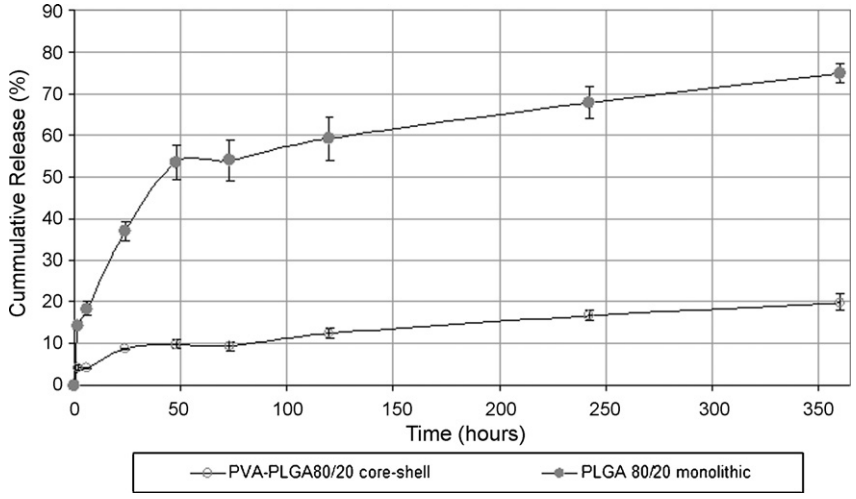

Fig. 10. Release profile of metoclopramide salt from PLGA monolithic and PVA–PLGA core–shell fibers.

clearly seen, as it becomes rate-controlling. In other words, the diffusion through the PLGA 80/20 is more facile than the partitioning of the drug into the PLGA shell; hence we see overall suppression of release, both initially and at later stages.

As is well known, drug release in reservoir-membrane systems at steady-state follows the equation:

$$M(t) = \left[\frac{2\pi hDKC_s}{\ln(r_0/r_i)}\right] \times t, \quad \text{for cylindrical fibers}$$

where $M(t)$ is the amount of drug released at time t; A = surface area; l is the thickness; h is the height of the cylinder; r_0 and r_i are the radii of the total fiber and of the core, respectively; D is the diffusion coefficient of the drug through the shell polymer (or the membrane polymer); K is the partition coefficient for the drug, from reservoir to membrane (from core to shell); C_s is the steady-state concentration.

In terms of the equation, the observations shown in Figs. 7–10 may be summed up as follows:

(a) For PVA–PLLA, $D \ll K$, hence diffusion through the PLLA shell controls the release, so no effect of a shell PLLA is seen in the release (compared to a PLLA monlith). The release is relatively low due to the high T_g of PLLA.
(b) In the case of PVA–PCL, there is effectively no partitioning because of the porosity of the PCL, which allows for direct access of release medium to the core PVA. Thus the release is mostly a burst release, and is rapid. There is some indication that as we increase the concentration of the shell solution, porosity is decreased (Fig. 8).
(c) It is only in the case of PVA–PLGA that the true partitioning effect is seen, indicating that the rate-controlling factor is partitioning. Thus $K < D$ in this case for the core–shell fibers, and the release rate decreases dramatically when the shell is present.

These data highlight some important requirements to be satisfied in order for effective partition control of drug release:

(1) There must be sufficient difference in hydrophilicity between core and shell, but not excessively so, as that may lead to a hollow core as has been observed for PEO cores, which are much more hydrophilic than 99% hydrolyzed PVA. Dror et al. (2008) have observed the formation of such hollow fibers in PEO–PCL core–shell system when they attempted to localize enzymes in the core. Dayal and Kyu (2006) have demonstrated theoretically that when core and shell solutions are immiscible, and when shell solvent evaporates faster than the core solvent, a hollow fiber is obtained owing to the formation of a sharp interface. The core and shell polymers, however, must show sufficient interfacial compatibility in order to prevent delamination at the interface.
(2) The drug must be much more soluble in the core than in the shell.
(3) The shell polymer spinning conditions are important: polymer concentration must be high enough to minimize pore formation, as excessive solvent leads to pore formation during evaporation. The minimum concentration appears to be around 10% (w/v), although this may vary from polymer to polymer.
(4) The diffusion through the shell polymer must not be too slow; otherwise this diffusion dominates the release. In this instance, there is no advantage of using that polymer as a shell over the monlith.

3.5. Comparison to earlier work

Jiang et al. (2005, 2006) had reported the use of core–shell fiber constructs for controlled release of proteins. The thrust of their work was to incorporate the protein (bovine serum albumin or BSA) in the core without other excipients, i.e. make the protein itself the core fiber, and then modulate its release by loading and by manipulation of the shell composition. It is interesting to note that Jiang et al. (2006) also used PCL as the shell polymer, with varying amount of PEG added to the shell. An evaluation of their protein release data shows that even with pure PCL as the shell, the protein burst release is still significant (~25–30%) which is attributed to the porosity of the PCL. Diffusion of the BSA protein should be low through the PCL shell; hence the only explanation for the observed burst is the porosity of the shell. Thus even using a high concentration of 300 mg/ml (~30%) of a lower-MW PCL (42,500 g/mole) for the shell spinning, Jiang et al. were unable to suppress pore formation in the PCL.

The addition of PEG to the PCL further increases the porosity leading to progressively higher bursts with added PEG. From the data presented, it appears that the various formulations (different BSA loadings with PCL shell; same BSA loading, different PCL–PEG shell compositions) only differ in the extent of burst release; subsequent release rates appear to be similar, as would be expected by a mechanism involving predominantly the diffusion of the BSA through water-filled pores. Nevertheless, Jiang et al. successfully reported suppression of burst using lower protein loadings.

Another point to be noted here is that we believe that Jiang et al.'s choice of BSA is somewhat fortuitous as BSA is a relatively hydrophobic protein, which leads to good interfacial compatibility with the PCL shell. Other proteins, predominantly hydrophilic, will exhibit a hollow tubular core as has been seen with PEO cores (Theron et al., 2004).

What we believe we have shown here is to highlight the conditions under which partitioning can be rate-controlling for a hydrophilic drug in a hydrophilic core/hydrophobic shell construct. Since electrospun fibers are small in diameter and possess high surface area, they present huge challenges in producing a well-defined core–shell structure sufficient for an effective reservoir/membrane system to be set up. We have shown that, in particular, that minimizing the porosity of the shell is essential in ensuring efficient drug partitioning into the core. Unless shell porosity is minimized, hydrophilic entities in the core will release through water-filled channels rather than through the "membrane" shell polymer. At the other extreme, if a glassy polymer is used as shell, with T_g's well above the 37 °C used for release measurements, diffusion through this dominates the release, with no benefit derived from a core–shell construct in this case. The optimum conditions for obtaining partitioning control are therefore minimum porosity of the shell polymer; a reasonably fast diffusional release through the shell polymer and sufficient interfacial compatibility of the core and shell polymers.

4. Conclusion and future work

In this study, drug loaded core–shell fibers have been prepared using biodegradable polymers and their release profiles have been compared with those of monolithic fibers made from the same polymers. The work clearly shows the sensitivity of the observed release to various parameters, related to both process and material, and suggests strategies for release control using partitioning in the core–shell structure. Further studies would aim to compare the release profiles of proteins and plasmid DNA and for different choices of core and shell polymers so as to develop further understanding of the core–shell fibers systems for drug and protein delivery applications.

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References

Boland, E.D., Wnek, G.E., Simpson, D.G., Pawlowski, K.J., Bowlin, G.L., 2001. Tailoring tissue engineering scaffolds using electrostatic processing techniques—a study of poly(glycolic acid) electrospinning. J. Macromol. Sci. A: Pure Appl. Chem. A38, 1231–1243.

Casper, C.L., Stephens, J.S., Tassi, N.G., Chase, D.B., Rabolt, J.F., 2004. Controlling surface morphology of electrospun polystyrene fibers: effect of humidity and molecular weight in the electrospinning process. Macromolecules 37, 573–578.

Dayal, P., Kyu, T., 2006. Porous fiber formation in polymer–solvent system undergoing solvent evaporation. J. Appl. Phys. 100, 043512.

Dror, Y., Kuhn, J., Avrahami, R., Zussman, E., 2008. Encapsulation of enzymes in biodegradable tubular structures. Macromolecules 41, 4187–4192.

Dror, Y., Salalha, W., Avrahami, R., Zussman, E., Yarin, A.L., Dersch, R., Greiner, A., Wendorff, J.H., 2007. One-step production of polymeric microtubes by co-electrospinning. Small 3, 1064–1073.

He, C.L., Huang, Z.M., Han, X.J., Liu, L., Zhang, H.S., Chen, L.S., 2006. Coaxial electrospun poly(L-lactic acid) ultrafine fibers for sustained drug delivery. J. Macromol. Sci. B: Phys. 46, 515–524.

Huang, Y.Y., Chung, T.W., Tzeng, T.W., 1999. A method using biodegradable polylactides/polyethylene glycol for drug release with reduced initial burst. Int. J. Pharm. 182, 93–100.

Jeong, Y.Y., Kang, M.K., Sun, H.S., Kang, S.S., Kim, H.W., Moon, K.S., Lee, K.J., Kim, S.H., Jung, S., 2004. All-*trans*-retinoic acid release from core–shell type nanoparticles of poly(ε-caprolactone)/poly (ethylene glycol) diblock copolymer. Int. J. Pharm. 273, 95–107.

Jiang, H., Hu, Y., Li, Y., Zhao, P., Zhu, K., Chen, W., 2005. A facile technique to prepare biodegradable coaxial electrospun nanofibers for controlled release of bioactive agents. J. Control. Release 108, 237–243.

Jiang, H., Hu, Y., Zhao, P., Li, Y., Zhu, K., 2006. Modulation of protein release from biodegradable core–shell structured fibers prepared by coaxial electrospinning. J. Biomed. Mater. Res. B 79, 50–57.

Jing, Z., Lixin, Y., Qizhi, L., Xuefei, Z., Huili, G., Xiuling, X., Xuesi, C., Xiabin, J., 2005. Influence of the drug compatibility with polymer solution on the release kinetics of electrospun fiber formulation. J. Control. Release 105, 43–51.

Kenawy, E.-R., Abdel-Hay, F.I., El-Newehy, M.H., Wnek, G.E., 2007. Controlled release of ketoprofen from electrospun poly(vinyl alcohol) nanofibers. Mater. Sci. Eng. A 459, 390–396.

Kenawy, E.-R., Bowlin, G.L., Mansfield, K., Layman, J., Simpson, D.G., Sanders, E.H., Wnek, G.E., 2002. Release of tetracycline hydrochloride from electrospun poly(ethylene-co-vinylacetate), poly(lactic acid), and a blend. J. Control. Release 81, 57–64.

Kim, K., Luu, Y.K., Chang, C., Fang, D., Hsiaoa, B.S., Chu, B., Hadjiargyrou, M., 2004. Incorporation and controlled release of a hydrophilic antibiotic using poly(lactide-co-glycolide)-based electrospun nanofibrous scaffolds. J. Control. Release 98, 47–56.

Li, D., Xia, Y., 2004. Electrospinning of nanofibres—reinventing the wheel? Adv. Mater. 16, 1151–1170.

Li, W.J., Cooper Jr., J.A., Mauck, R.L., Tuan, R.S., 2006. Fabrication and characterization of six electrospun poly(a-hydroxy ester)-based fibrous scaffolds for tissue engineering applications. Acta Biomater. 2, 377–385.

Li, W.J., Tuli, R., Huang, X., Laquerriere, P., Tuan, R.S., 2005. Multilineage differentiation of human mesenchymal stem cells in a three-dimensional nanofibrous scaffold. Biomaterials 26, 5158–5166.

Qian, F., Szymanski, A., Gao, J., 2001. Fabrication and characterization of controlled release poly(D,L-lactide-co-glycolide) millirods. Int. J. Pharm. 55, 512–522.

Reznik, S.N., Yarin, A.L., Zussman, E., Bercovici, L., 2006. Evolution of a compound droplet attached to a core–shell nozzle under the action of a strong electric field. Phys. Fluids 18, 062101.

Srikar, R., Yarin, A.L., Megaridis, C.M., Bazilevsky, A.V., Kelley, E., 2008. Desorption-limited mechanism of release from polymer nanofibers. Langmuir 24, 965–974.

Sun, Z.C., Zussman, E., Yarin, A.L., Wendorff, J.H., Greiner, A., 2003. Compound core–shell polymer nanofibers by co-electrospinning. Adv. Mater. 15, 1929–1936.

Tan, S.H., Inai, R., Kotaki, M., Ramakrishna, S., 2005. Systematic parameter study for ultra-fine fiber fabrication via electrospinning process. Polymer 46, 6128–6134.

Theron, A., Zussman, E., Yarin, A.L., 2001. Electrostatic field-assisted alignment of electrospun nanofibres. Nanotechnology 12, 384–390.

Theron, S.A., Zussman, E., Yarin, A.L., 2004. Experimental investigation of the governing parameters in the electrospinning of polymer solutions. Polymer 45, 2017–2030.

Zilberman, M., 2007. Novel composite fiber structures to provide drug/protein delivery for medical implants and tissue regeneration. Acta Biomater. 3, 51–57.