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A simple and versatile method for microencapsulation of anti-epileptic drugs for focal therapy of epilepsy

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Abstract: Nearly 30% of epilepsy cases cannot be adequately controlled with current medical treatments. The reasons for this are still not well understood, but there is a significant body of evidence pointing to the blood-brain barrier. Resective surgery can provide an alternative method of epilepsy control; however this treatment option is not suitable for most epilepsy sufferers. Local drug delivery through micro-injection to or implantation into the brain provides an innovative approach to bypass the blood-brain barrier for epilepsy treatment. In order to develop effective local delivery systems for anti-epilepsy drug (AED), we have prepared a variety of core-shell microcapsules via electrojetting, where a more hydrophobic polymer shell acts as a physical barrier to control the rate of drug release from the drug-loaded polymeric core. The resulting microcapsules demonstrate highly drug encapsulation efficiency, narrow size distribution and uniform morphology. Moreover, the release rate of AED can be modulated by controlling the morphologies of the core-shell microcapsules.

Key Words: Drug delivery; Epilepsy; Electrojetting; Lacosamide; Microcapsules

Introduction

Epilepsy is a long-term neurological disorder, affecting more than 60 million people worldwide. It is characterised by recurrent and unpredictable seizures, which can cause loss of consciousness, falls and injury, psychosocial disability, and even mortality. Medication provided via oral administration is the first approach to epilepsy treatment, but controls only up to 70% of the cases, whilst the rest of the patients remain incompletely responsive to medication[1, 2]. The reasons for this are not yet fully understood, but there is significant body of evidence pointing to the blood-brain barrier (BBB)[3]. The BBB protects the brain from harmful blood-borne substances and microorganisms by separating the brain parenchyma from the circulating blood. Such self-protection also poses an obstacle to drug delivery to the brain. Nearly 100% of high molecular weight drugs and >98% of low molecular weight drugs are excluded from the brain[4-6]. For instance, a typical dosage of an antiepilepsy drug (AED), such as lacosamide (used in this study), is 400 -500 mg per day[7, 8] by oral administration. However, the actual amount of lacosamide arriving at the sites of seizures is very limited due to the limited ability of the drug to cross the BBB[3]. Moreover, this high systemic dosage causes serious whole body side-effects, such as rashes, nausea and weight changes.

For patients whose seizures cannot be controlled by medications, surgery represents an alternative option, which can be provided only to appropriately selected patients, where the seizure origin in the brain can be localized. In addition, a comprehensive pre-surgical assessment must be conducted in order to ensure the benefits of the operation. Following surgical therapy, the patients still need to take AEDs for a long time to prevent epilepsy relapse[9, 10].

To improve epilepsy control, local drug delivery through micro-injection or implantation in the brain to bypass the BBB may offer an innovative approach to improve the efficacy of medication. This approach can significantly reduce the dosage of AEDs, while concurrently minimising the side effects associated with systemic administration of AEDs[11, 12]. In addition, compared to surgical resection, direct injection or implantation would significantly reduce potential brain damage[13].

An ideal local drug delivery system should be biocompatible, biodegradable and exhibit an optimal drug release profile pertaining to the targeted application. It should also be amenable to fabrication and large scale production. Poly(lactic-*co*-glycolic acid) (PLGA) has been intensively studied for local drug delivery[14-16]. In particular, it has been explored in treating central nervous system disorders, such as Alzheimer's[17, 18] and Parkinson's[19, 20] diseases, as well as in treating brain injury[21], demonstrating excellent brain biocompatibility. Lacosamide, the R-enantiomer of 2-acetamido-N-benzyl-3-methoxypropionamide, is a novel antiepilepsy drug. Based on the efficacy and therapeutic index observed in a range of animal models of epilepsy at the National Institutes of Health (NIH) Anticovulsant Screening Program, lacosamide warranted further evaluation and was subsequently developed as an AED for both oral and intravenous use. It suggests that lacosamide has a dual action underlying its anticonvulsant and analgesic. It's also found that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels without affecting fast inactivation[22]. In terms of material fabrication, electrojetting, such as electrospinning and electrospraying, has attracted tremendous interesting in recent years[23-28]. It is a low-cost and versatile technique for uniform fabrication of polymer structures ranging from nanoscale to microscale[29-31]. However, only limited studies have been undertaken on the electrojetted systems in terms of morphology, drug loading efficiency and drug release characteristics[31, 32]. Moreover, to the

best of our knowledge, no study has yet to be reported on core-shell structured electrojetted systems.

Herein we report a novel electrojetting technique for fabrication of core-shell microspheres and microfibers, where AED-laden polymer cores are surrounded by drug-free polymer shells that act as a barrier to regulate drug release characteristics. A variety of core-shell PLGA/lacosamide microcapsules, including microflakes, flattened microspheres, microspheres, microspheres-fibers, beaded microfibers, and microfibers, have been developed with narrow size distribution and uniform morphology. These systems demonstrated high efficiency in drug encapsulation and sustained drug release characteristics, which makes them promising candidates as injectable microspheres and polymer implants for local drug delivery for epilepsy control.

Materials and methods

Materials

Poly(D,L lactic-*co*-glycolic acid) (PLGA) (M_w ~ 60,000 Da) with various molar ratio of lactide to glycolide, including PLGA 75/25 (lactide/glycolide = 75/25) and PLGA 85/15 (lactide/glycolide = 85/15), were purchased from Purac, Singapore, and used as received. Lacosamide, an anti-epilepsy drug, was provided by UCB Pharma Pty Ltd. All the others chemicals and reagents were purchased from Sigma-Aldrich.

Electrojetting (electrospinning and electrospraying)

A range of solutions of PLGA 75/25 and lacosamide were prepared as the core solutions for electrojetting. In these solutions, the ratio of polymer/drug (w/w) was kept constant at 10/1, while the polymer concentration varied from 0.75 to 15 wt%. A range of drug-free PLGA

85/15 solutions were prepared as the shell solutions for electrojetting, with the polymer concentration ranging from 0.5 to 10 wt%.

Electrojetting (electrospinning and electrospraying, respectively) was conducted at room temperature using an NANON-01A electrospinning system (MECC Co. Ltd, Japan). A coaxial spinneret with 0.2 mm core and 0.8 mm sheath nozzles were connected to the core and shell solutions. The distance from the spinneret tip to collector was maintained at 12 cm, and the applied voltage for electrospinning and electrospraying was 21 kV and 10 kV, respectively. The feed rate was 0.1 mL/h for the core solutions and 0.4 mL/h for the shell solutions. Aluminium foil was used to collect the fabricated core-shell microcapsules, and the samples were further dried in a vacuum oven at room temperature for 48 hours to remove any residual organic solvent.

Morphological and dimensional statistical analysis

The morphologies of the as-prepared microcapsules were examined using a Field Emission Scanning Electron Microscope (FESEM, JEOL JSM-7500FA). The samples were sputter-coated with 20 nm gold to avoid charge accumulation. Dimensional statistical analysis was conducted by analysis of the SEM micrographs using the imaging software, Leica Application Suite. All data were expressed as mean ± standard deviation (SD).

Determination of drug encapsulation efficiency

An extraction method was used to determine the drug encapsulation efficiencies of the as-fabricated core-shell microcapsules. Briefly, each sample (1 cm × 1 cm) was placed into 1 mL methanol for 12 hours, after which the methanol was removed and replenished with 1 mL of fresh methanol. This extraction procedure was repeated four times with each methanol

sample allowed to evaporate to leave residual drug behind which was reconstituted using artificial cerebrospinal fluid (aCSF, 0.866 wt% NaCl, 0.224 wt% KCl, 0.0164 wt% $MgCl_2 \cdot 6H_2O$, and 0.0206 $\cdot 6H_2O$ $CaCl_2 \cdot 6H_2O$ in 0.001M Phosphate Buffer Solution). Each aCSF sample was then analysed for drug content using HPLC (see below). The 4th reconstituted sample showed absence of drug indicating that the entire drug had been extracted from the electrojetted sample.

HPLC analysis was conducted on an Agilent 1260 Infinity HPLC system. The analytical column used was an Atlantis® T3 C18 column (5 μm, 250 mm × 4.60 mm). The mobile phase consisted of MilliQ water, acetonitrile (HPLC grade) and methanol (HPLC grade) (65:26.2:8.8, v/v/v). The mobile phase flow rate was 0.8 mL/min, and the UV-vis detection wavelength was 210 nm[33]. The amounts of released drug were calculated according to a pre-established calibration curve that was obtained by plotting the peak areas against respective concentrations of a range of standard lacosamide solutions prepared in aCSF.

In vitro drug release study

In vitro drug release was conducted in artificial cerebrospinal fluid (aCSF). Each sample (1 cm × 1 cm) was incubated in 1 ml of aCSF at 37 ^oC in a shaking water bath. At appropriate time intervals, the release medium was withdrawn and replaced with 1mL of fresh aCSF. The released samples were stored at -20^oC prior to the HPLC analysis for quantification of the amounts of the lacosamide released.

Results and discussion

Preparation of various forms of electrojetted core-shell microcapsules

Electrojetting, including electrospinning and electrospraying, represents a simple and versatile method for producing monodisperse polymeric spheres and fibres at the nano- and micro-scale[23, 34]. Electrojetting is governed by the interactions between the electrostatic repulsion induced by an applied electric field, and surface tension of a liquid droplet. When the electrostatic repulsion surpasses the surface tension to a critical point, liquid ejection will occur at the surface of the droplet. The liquid jet will undergo a whipping process, which leads to the formation of either fibres (electrospinning, as shown in **Figure 1a**), or spheres (electrospraying, as shown in **Figure 1b**) at the nano- or micro-scale. Therefore, the final electrojetted structure is determined by the electric force applied and the properties of polymer solutions. The polymer solution properties are governed by the molecular weight and concentration of the polymer, as well as the solvent properties.

In this study, PLGA 75/25 and lacosamide were used as the core structural materials, whilst PLGA 85/15, a more hydrophobic copolymer, was used as the shell material[35]. Chloroform was used as the solvent, with a low boiling point of 61.2 ^{o}C. By adjusting the applied voltage and screening of the concentrations of the core and shell solutions, microcapsules with various shapes (**Figure 2**), including microflakes, flattened microspheres, microspheres, microspheres-fibres, beaded microfibers, and microfibers, were successfully fabricated. These microstructures, together with their respective fabrication conditions, including the concentrations of the core and shell solutions and voltage, are summarised in **Table 1**. For electrospraying of microflakes, flattened microspheres, microspheres or microspheres-fibers, a 10 kV voltage was used, whereas for electrospinning of beaded microfibers or microfibers, a 21 kV voltage was used.

Morphological and dimensional statistical analysis

During the electrojetting process for fabrication of the microflakes or flattened microspheres, both the polymer concentrations in the core and shell solutions are very low (Table 1). This results in the rapid collapse of PLGA microcapsules during solvent evaporation and polymer solidification, to produce the microflakes and flattened microspheres with a rough, pitted and porous surface topography[36]. At higher PLGA concentrations, such as 6 wt% for the core solution and 4 wt% for the shell solution, microspheres are produced, exhibiting a much smoother surface. Further increasing the PLGA concentrations to 7.5 wt% for the core and 5 wt% for the shell results in concurrent formation of microspheres and microfibers, where the diameters of fibres are much thinner than those of the microspheres. The portion of the microfibers in the microcapsules increases with increasing the polymer concentrations. When the polymer concentration reaches 15 wt% for the core and 10 wt% for the shell, only microfibers are produced. Our work demonstrates a critical role of both the polymer concentrations of the core and shell solutions in controlling the shape and morphologies of the electrojetted core-shell microcapsules. A similar concentration effect has recently been reported in a range of PLGA microcapsules that were produced by electrojetting a single solution and thus do not possess the core-shell structures[31].

In order to evaluate the shape, size and size distribution of the as-prepared microcapsules, a Leica Application Suite was used to analyse the SEM images. The sizes of the microflakes, flattened microspheres, microspheres, microspheres-fibers, beaded microfibers, and microfibers are presented in **Figure 3a** with schematic representation shown in **Figure 3b** and the size distribution of each type of microcapsule is shown in **Figure 3c**. Each type of the electrojetted core-shell microcapsules exhibits a narrow size distribution and uniform morphology. With an increase in the PLGA concentrations, the dimension of the respective microcapsules firstly increased, and then decreased in the case of microfibers. The diameters

are 2.26±0.67 μm for the microflakes, 2.67±0.46 μm for the flattened microspheres, 4.42±1.08 μm for the microspheres, 5.35±0.94 μm for the microspheres-fibres, 7.02±1.45 μm for the beaded microfibers, and 1.11±0.43 μm for the microfibers, respectively.

In accordance with Hartman's study[37], the dimension of PLGA microspheres formed using electrospraying is governed by the surface tension of the polymer solution, as shown in Equation (1):

$$d \sim \left(\frac{\rho \varepsilon_0 Q^3}{\gamma K}\right)^{1/6} \quad (1)$$

Where d is the droplet size, ρ is the density of solution, ε_0 is the permittivity of vacuum, Q is the liquid flow rate, γ is the surface tension of solution in ambient air, and K is the liquid conductivity. Increasing the polymer concentration leads to an increase in the solution viscosity, and a reduction in the surface tension (γ), and consequently an increase in microsphere size (d) (Equation 1)[37]. When the polymer concentration becomes sufficiently high, the solution can endure continuous and longer stretching from the nozzle tip to the collector, which gives rise to much thinner microfibers through a mechanism of electrospinning.

Drug encapsulation efficiency

It is shown in **Table 1** that all the fabricated core-shell microcapsules exhibit > 90% drug loading efficiencies. The core-shell microfibers demonstrate the highest drug loading efficiency (99.2±5.4%). These encapsulation efficiencies are greater than those prepared using other techniques, including emulsion, suspension, and emulsion polymerization[38], solvent evaporation[38, 39], spray drying[40], layer-by-layer[41]. This can be ascribed to i) the inherent core-shell structures where drug is encapsulated in the core and further protected by

a shell of more hydrophobic polymer and ii) the fast solidification of the microcapsules at room temperature due to the use of a low boiling point solvent, chloroform[31, 42].

In vitro drug release study

The representative *in vitro* release profiles of lacosamide from the fabricated PLGA microflakes, microspheres, microspheres-fibers, and microfibers are shown in **Figure 4**. The sustained release characteristics demonstrated by all the microcapsules could be attributable to their core-shell structures, where the drug-free polymer shells presents an additional barrier to the drug elution from the core[35]. The release profiles varied significantly with the shape and morphologies of the microcapsules. The microflakes exhibited the most rapid release characteristics, with > 96% of the encapsulated lacosamide being eluted within ~43 hours. Within the same period, the cumulative release of the lacosamide from the microspheres, microspheres-fibres, and microfibers, was approximately 75%, 60%, and 35% of the respective total drug loading. Compared to the microflakes, microspheres, and microsphere-fibers, microfibers exhibit significantly less initial burst release.

It is also noted that there is no significant mass loss in the microcapsules after the long-time incubation in aCSF (104 days), other than that arising from the drug elution. This suggests minimal polymer degradation of the electrojetted microcapsules taking place within this period, which also indicates that the drug release from these microcapsules is predominantly diffusion controlled. The morphology and dimension of the PLGA microcapsules had a significant influence in the lacosamide release characteristics. For the microcapsules dominant by a sphere/particulate shape, including microflakes, microspheres, microspheres-fibers, the release rate decreased with increasing the microcapsule dimension (**Figure 3b and Figure 4**). With an increase in the sizes of the microcapsules, the surface area to volume

ratios of the microcapsules decrease, and this leads to slower water penetration rates into the microcapsules and thus slower drug release profiles.

These microcapsules can serve as an injectable microparticulate systems or polymer implants, for local pharmaceutical intervention of epilepsy, as well as treatments in other neurological disorders, such as Parkinson's disease, Huntington's disease and Alzheimer's disease. Compared to systemic administration that requires high dosages, local implantation or injection using our drug-eluting microcapsules can significantly reduce the dosage and side effects. Moreover, our drug release study demonstrated that the daily release dosage of our systems can be readily tailored by varying the shape and size of the microcapsules.

Conclusions

In summary, a variety of core-shell structured PLGA microcapsules containing an anti-epilepsy drug, lacosamide, have been fabricated by a novel electrojetting technique. These microcapsules, including microflakes, flattened microspheres, microspheres, microspheres-fibers, beaded microfibers, and microfibers), all demonstrated narrow size distribution and uniform morphology, high efficiency of drug encapsulation and sustained drug release characteristics. The release profile of lacosamide varies with the morphologies and shape of the core-shell microcapsules, and thus can be readily controlled over long periods of time.

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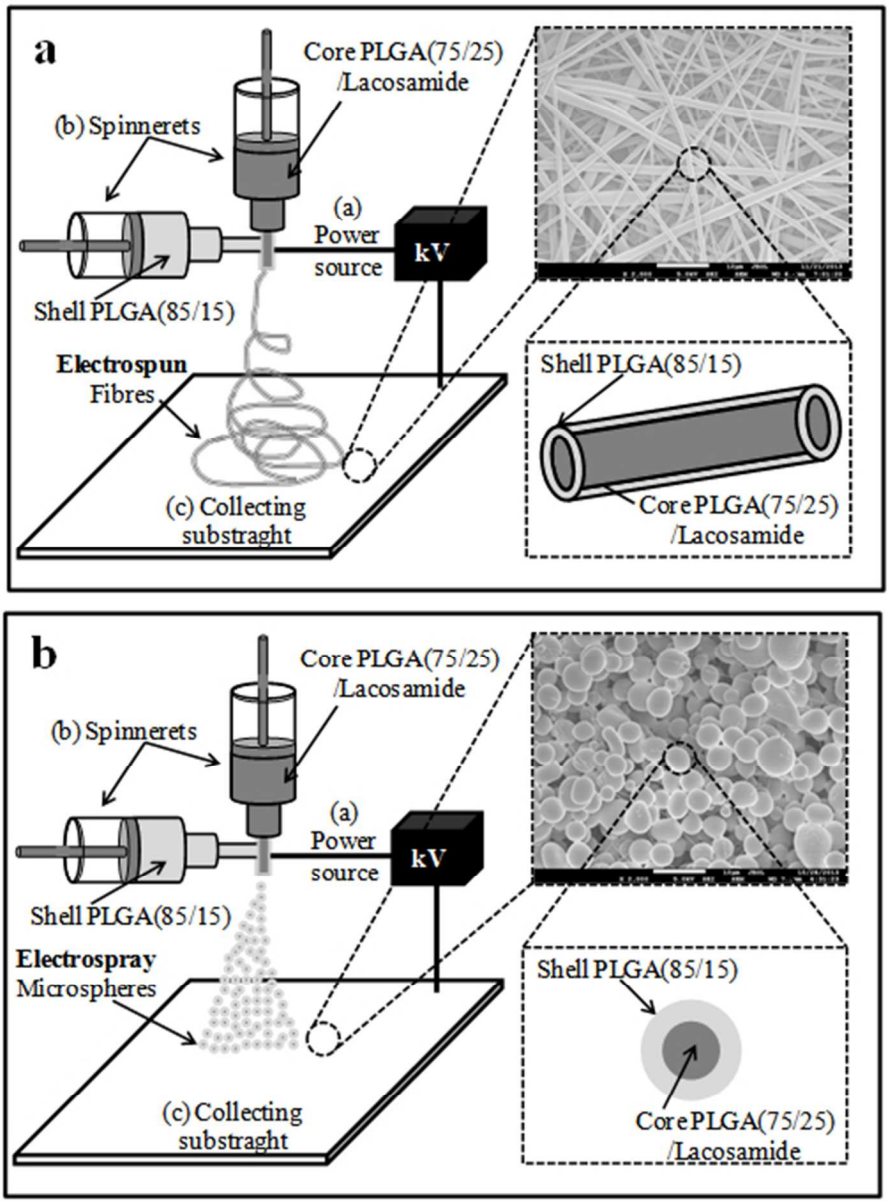
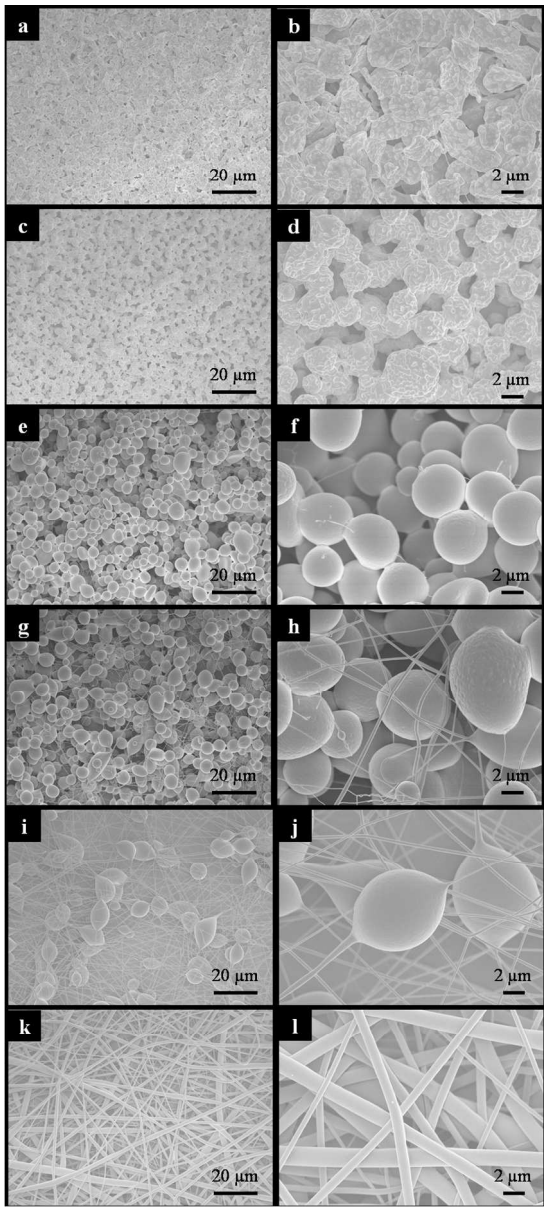
Sample Code	Core PLGA (75/25) concentration (wt %)	Shell PLGA (85/15) concentration (wt %)	Applied Voltage (kV)	Type of microcapsule formed	Drug loading (%)
S0w	0.75	0.5	10	Microflakes	90.6±5.2
S2w	3	2	10	Flattened microspheres	91.1±8.1
S4w	6	4	10	Microspheres	94.0±3.5
S5w	7.5	5	10	Microspheres-fibers	95.3±3.0
S8w	12	8	21	Beaded microfibers	94.9±4.2
S10w	15	10	21	Microfibers	99.2±5.4

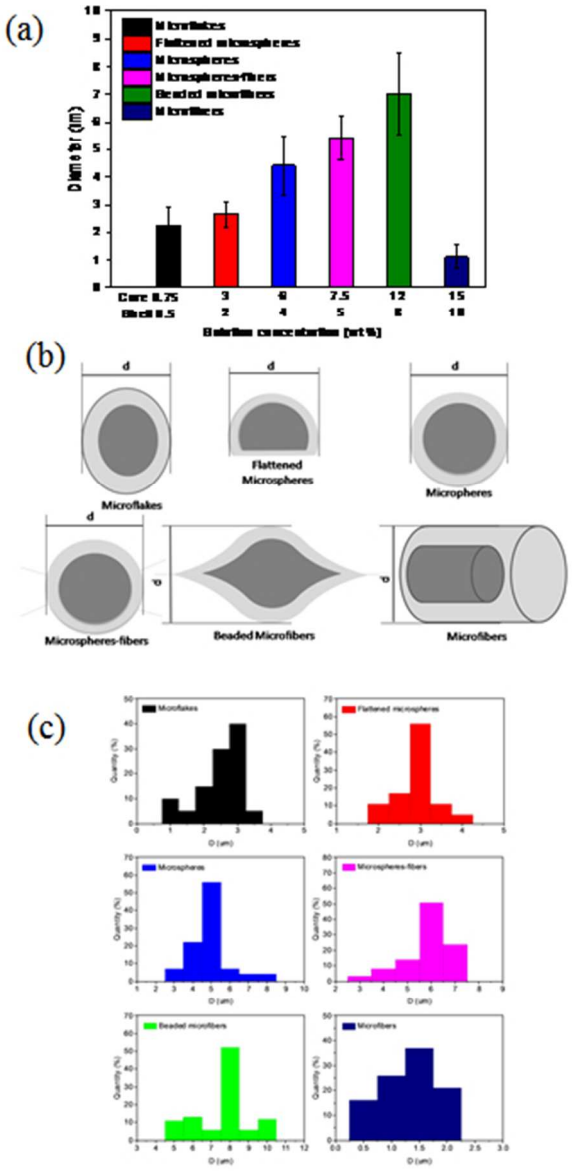
Microcapsules with various structures, drug loading, and their respective fabrication conditions.
162x73mm (96 x 96 DPI)



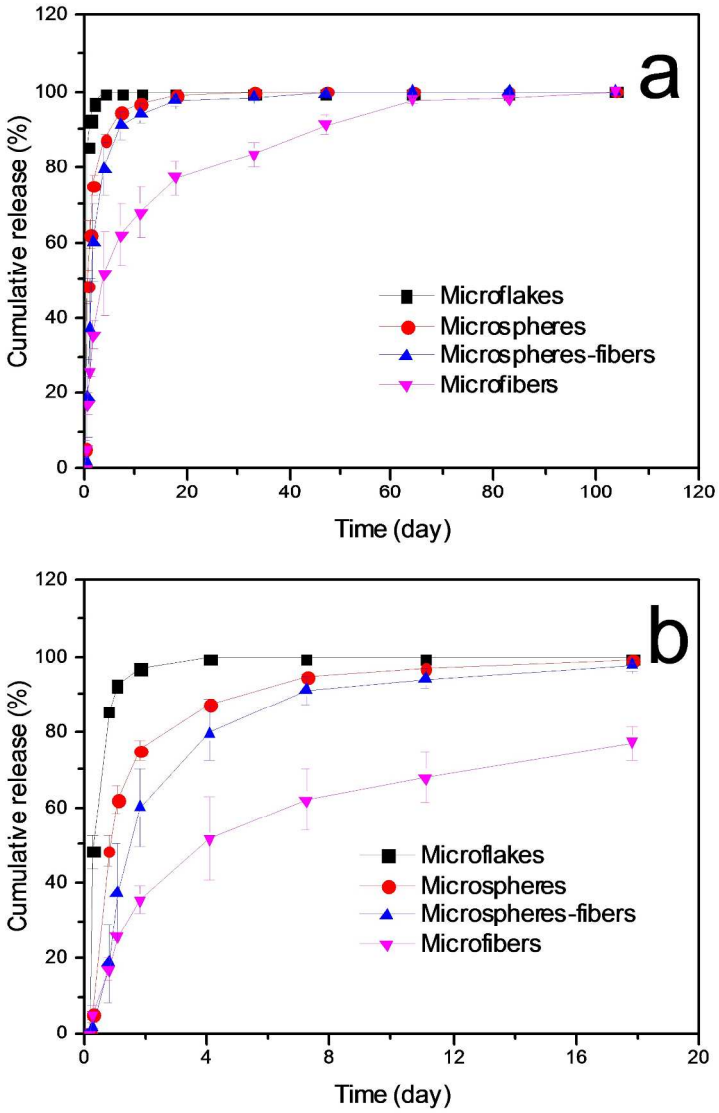
Schematic illustration of the electrojetting setup, including a) electrospinning of microfibers and b) electrospraying of microspheres.
135x179mm (96 x 96 DPI)



Scanning Electron Microscope (SEM) images of various PLGA microcapsules; a, b) Microflakes, c, d) Flattened microspheres, e, f) Microspheres, g, h) Microspheres-fibers, i, j) Beaded microfibers, k, l) Microfibers.
244x545mm (96 x 96 DPI)



Size of the fabricated microflakes (a), flattened microspheres, microspheres, microspheres-fibers, beaded microfibers, and microfibers. Schematically illustration of the detection points of the sizes of the microcapsules (b). Size distribution of each type of microcapsule (c).
93x187mm (96 x 96 DPI)



Cumulative release of lacosamide from the fabricated PLGA microcapsules in aCSF (pH 7.4) at 37 oC over 104 days (a). The release profiles of the microcapsules in the first 20 days (b).
717x952mm (96 x 96 DPI)