*Research article*

# Influence of a Non-ionic Surfactant on the Release of Rhodamine B from Poly(vinyl) Alcohol/Polyoxalate/Span-80 Composite Nanofibers Prepared by Emulsion Electrospinning

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## Abstract

Controlling drug release using a nanocomposite method is crucial; however, burst release must be avoided in order to obtain effective controllable drug release. In this study, poly(vinyl) alcohol/polyoxalate/Span-80 (PVA/ POX/ Span-80) composite nanofibers loaded with Rhodamine B were produced using emulsion electrospinning. The objective of this work was to evaluate the cooperative roles of POX and Span-80 on nanofibrous scaffold stability and drug release regulation by monitoring Rhodamine B release performance from electrospun composite nanofibers. The microstructure and hydrophilic properties of the emulsion electrospun nanofibers were studied using scanning electron microscopy (SEM), water contact angle, and swelling tests. According to the results, increasing the POX content had a significant effect on the size of nanofibers. The water contact angles increased as the POX content increased. The release of Rhodamine B was governed by a two-stage diffusion mechanism that was greatly influenced by PVA/POX ratios and Span-80. To compare release behavior, non-emulsion electrospun nanofibers without Span-80 were prepared as control samples. Emulsion nanofibers were found to release at a slower rate than non-emulsion nanofibers. The *in vitro* release profiles revealed that Rhodamine B was released from emulsion electrospun fibers in a sustainable manner and that no initial burst release was observed. These findings imply that emulsion electrospun nanofibers can potentially be used to deliver drugs, nutraceuticals, and fragrances in a prolonged manner.

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## 1. Introduction

Electrospinning is a versatile and effective technique for producing a fibrous scaffold with diameters ranging from micrometers to nanometers [1]. Nanofibers are generated in the electrospinning process when a polymer solution is electrified until the electrostatic force overcomes the surface tension of the polymer solution. A polymer jet is then generated and stretched to create non-woven nanofibers [2]. This top-down manufacturing approach generates matrix nanofiber scaffolds with a high surface area and a high porosity that may be employed in a variety of biomedical applications, including tissue engineering, wound healing, and drug delivery [3].

The polymer employed in the formulation, as well as its concentration and physicochemical qualities, are important for the creation of electrospun fibers with the desired properties [2]. PVA is a nontoxic and hydrophilic polymer [4]. Electrospun nanofibers made from PVA have been employed in tissue engineering applications [5]. This is due to PVA's great chemo-thermal stability and outstanding biocompatibility. Furthermore, because PVA scaffolds are not biodegradable in most physiological circumstances, they are suitable for long-term or permanent scaffolds in tissue engineering. However, its great hydrophilicity can result in water adsorption. This can cause the PVA nanofibers to swell and combine, losing their fibrous shape. To address this issue, the post-electrospun treatment and crosslinking method were used. However, the post-electrospun treatment and crosslinking technique may lead them to lose porosity structure [6].

The tuning of nanofiber morphology, porosity, and chemical composition facilitates finely controlled drug release strategies [7]. The drug released from nanofibers has been widely studied in order to achieve a predictable release. Encapsulated drugs that are evenly distributed in nanofibers can be released very quickly due to their high specific surface areas and short diffusion lengths [8, 9]. This unpredictable drug release manner is a major drawback of monolithic fibers. However, composite polymeric nanofibers can improve stability and offer new nanofiber features; nonetheless, there are still issues with drug release [10]. Therefore, emulsion electrospinning was proposed to produce core-shell nanofibers with reduced burst release and longer release time. Notably, the inner core of these nanofibers has been effectively used to encapsulate drugs, proteins, and growth factors [11]. During the stretching and solidification processes, the rapid evaporation of the oil phase effectively retains the majority of the drug within the fibers, preventing its escape onto the fiber surfaces and thereby avoiding drug burst release [12, 13].

Surfactants, or surface-active agents, play a crucial role in the processes of emulsification and droplet stabilization. When surfactants are introduced into an emulsion system, they effectively reduce the interfacial tension between the immiscible liquids. Moreover, surfactants have the capacity to envelop microdroplets, preventing their coalescence [14]. The choice of surfactant and its concentration can have a significant impact on the properties and performance of the resulting emulsion nanofibers [15]. Ionic surfactants have the ability to increase the net charge density, thereby influencing the morphological and mechanical properties of nanofibers [16, 17]. On the other hand, non-ionic surfactants serve to stabilize the interface between immiscible liquids, enhancing the electrospinnability process and enabling the production of uniformly strructured nanofibers suitable for various applications, including drug release [18].

In our previous work, we established that POX, a hydrogen peroxide-responsive polymer, could be used in a composite with PVA and significantly minimize the burst release of Rhodamine B from the composite nanofibers [19, 20]. The purpose of this study was to evaluate the role of nonionic surfactants on the properties of nanofibers in terms of modulating drug release, thereby improving sustained drug release. Emulsion electrospinning was used to create a series of composite nanofibers (PVA/POX/Span-80). As a model compound, Rhodamine B was impregnated into nanofibers to monitor drug release (Figure 1). Nanofibers composed of PVA and POX were prepared and used as non-emulsion nanofiber control samples.

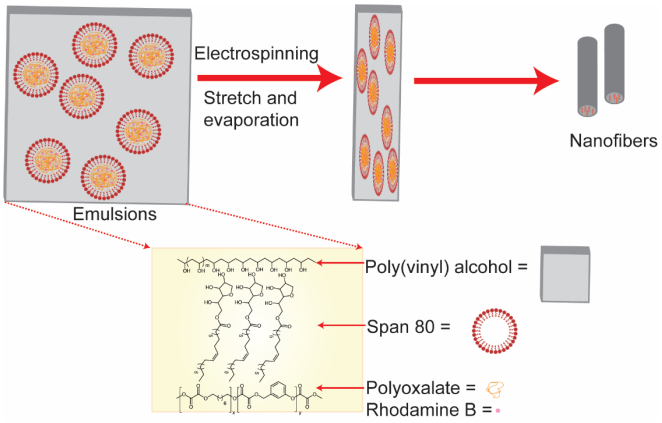


**Figure 1.** Schematic representation of Rhodamine B-loaded PVA/POX-Span-80 composite nanofiber formation during O/W emulsion electrospinning

## 2. Materials and Methods

### 2.1 Materials

Rhodamine B and Poly(vinyl alcohol) (PVA) (98-99% hydrolyzed; typical Mw, 77,000-82,000) were purchased from Sigma-Aldrich (MO, USA). PBS buffer and sorbitan monooleate (Span-80) were obtained from Sigma and were used without further purification. According to our previous report, POX (prepared from 1,8-octanediol, 4-hydroxybenzyl alcohol, and oxalyl chloride) was synthesized [19]. As determined by gel permeation chromatography, its molecular weight (Mw) and polydispersity (PD) were 15,000 and 2.72, respectively.

### 2.2 Preparation of oil-in-water emulsions containing Rhodamine B

POX and Rhodamine B emulsions were prepared by dissolving POX and Rhodamine B in 5 mL of dichloromethane at concentrations of 3 wt% and 1 wt%, respectively. After that, 5 µL of Span-80 was added to the previously prepared organic mixture to produce the oil solution. To make a 10 wt% aqueous solution, PVA was dissolved in 10 mL of distilled water. Following that, 1 mL oil solution was dropwise added into 10% PVA solution (or the water solution) with PVA/POX in varied ratios, i.e., 10/0, 9/1, 8/2, 7/3, 6/4, and 5/5. To obtain uniform emulsions, the emulsion mixture was stirred for 5 h. Non-emulsion electrospun nanofibers were made in a similar manner but without the addition of Span-80 as control samples.

### 2.3 Electrospinning process

The polymer solution was placed into a plastic syringe fitted with an 18-gauge (1.270 mm in diameter) stainless steel needle. The needle was attached to a high-voltage supply of 20 kV. The solution was fed at a rate of 1.0 mL/h. The distance between the needle's tip and the flat aluminum foil collector was fixed at 15 cm.

### 2.4 Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was used to examine the morphologies of the electrospun PVA/POX-Span-80 nanofibers (LEO VP1450, UK). Using Nano VB software, the average fiber diameter and distribution of 250 randomly selected fibers were observed from their SEM micrographs (Khon Kaen University, Thailand).

### 2.5 Water contact angle measurements

The water contact angles of the PVA/POX-Span-80 nanofibers were measured using a FTA1000 contact angle analyzer (FTA, USA). PVA/POX-Span-80 nanofibers were first cut into 1 cm × 1 cm square specimens before being put on a testing plate. The prepared specimens were then carefully dropped with 0.02 mL of DI water. The contact angles between water droplets and nanofiber mat specimens were calculated using photos taken at various intervals (1, 5, 10, 30, and 60 seconds). At least five measurements were taken in various positions for each specimen.

### 2.6 Swelling studies

The swelling ratio was used to calculate the capacity for water adsorption. Samples were weighed ($W_0$) and immersed in double distilled water for 24 h before being weighed (W). The swelling ratio (Q) was calculated using the following equation:

$$Q = \frac{W - W_0}{W} \times 100\% \quad (1)$$

### 2.7 *In vitro* drug release studies

The release of Rhodamine B in the buffer solution was measured using a fluorospectrophotometer (JASCO spectrophotometer FP-8200). At 37ºC (pH~7.4), each Rhodamine B-loaded nanofiber sample (5 mg) was incubated in 5 mL of phosphate buffered saline. Following the required incubation period, the buffer was aspirated, and measurements were taken to determine the amount of Rhodamine B released. Each sample was then incubated with a fresh buffer solution (5 mL). The excitation wavelength was 500 nm, and the emission wavelength was 582 nm. Using the Rhodamine B calibration curve in the same buffer, the fluorescence intensity of Rhodamine B was converted to its concentration. The accumulated weight and the relative percentage of released Rhodamine B were then calculated as a function of incubation time.

## 3. Results and Discussion

### 3.1 Morphological examination

Surfactants are used in emulsion electrospinning to stabilize the dispersed particles during emulsification [16]. Surfactants can reduce the surface tension of polymer solutions during electrospinning processes, which reduces or prevents droplet formation and results in more uniformly oriented fibers [21, 22]. Span-80, a non-ionic surfactant, was chosen for this study because it has been commonly utilized in food products and oral pharmaceuticals. SEM was used

to analyze the morphologies of the produced composite nanofibers. Figure 2 shows SEM images of electrospun Rhodamine B-loaded PVA/POX-Span-80 composite nanofibers with various PVA/POX volume ratios (10/0, 9/1, 8/2, 7/3, 6/4, and 5/5). The fabricated fibers were all uniform and had smooth surfaces. No Rhodamine B crystals were found on the nanofiber surfaces, indicating that the Rhodamine B was finely integrated into the nanofibers. With the increase of POX in the nanofibers, the average diameter of the composite nanofibers increased from 175±32 nm to 403±76 nm. The average diameters of all composite nanofibers are summarized in Table 1. The dispersion of composite nanofiber diameters increased with increasing POX, as demonstrated for nanofibers with PVA/POX-Span-80 ratios of 6/4 and 5/5. The increase in nanofiber diameter could be attributed to an increase in the viscosity of the prepared polymer solution. This means that increasing the POX content influences the viscosity of the prepared polymer solution [20].

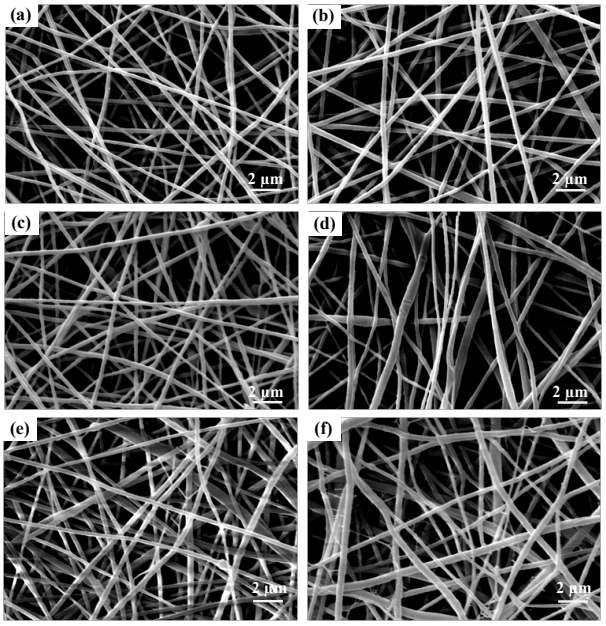


**Figure 2.** SEM images showing the morphologies of PVA/POX-Span-80 composite nanofibers at various PVA/POX ratios: 10/0 as spun (a), 9/1 (b), 8/2 (c), 7/3 (d), 6/4 (e) and 5/5 (f)

**Table 1.** Diameter and distribution of PVA/POX-Span-80 composite nanofibers with varying PVA/POX ratios

| Sample of PVA/POX | Average diameter (nm) | Diameter distribution (nm) |
|---|---|---|
| 10/0 | 175±32 | 85-255 |
| 9/1 | 214±63 | 96-297 |
| 8/2 | 238±47 | 118-339 |
| 7/3 | 247±38 | 112-356 |
| 6/4 | 392±82 | 95-684 |
| 5/5 | 403±76 | 107-692 |

## 3.2 Water contact angle characterization

The water contact angle is an indicator of the hydrophilicity of nanofiber mats, which can play a crucial role in their overall biomedical performances [23]. Nanofiber wettability can be determined using their water contact angle. As shown in Figure 3 and Table 2, the water contact angles of electrospun composite nanofibers with PVA/POX-Span-80 volume ratios of 5/5, 6/4, 7/3, 8/2, 9/1, and 10/0 as-spun were 66.22°, 47.85°, 35.50°, 27.08°, 24.77°, and 18.62°, respectively. The hydrophilicity was shown to decrease as the POX level increases. As expected, the composite nanofibers with a PVA/POX-Span-80 ratio of 10/0 had the highest hydrophilicity, as indicated by the smallest water contact angle. This is due to the hydrophilic property of PVA. Figure 4 depicts the swelling ratio of PVA/POX-Span-80 composite electrospun nanofibers at various ratios. Increased POX content was found to reduce the swelling ratio. This behavior corresponds to the observed water contact angle result. The water contact angle of the nanofibers decreased slightly with the addition of Span-80 as compared to the non-emulsion nanofibers (Table 2), which can be attributed to the presence of surfactants in the nanofibers. The surfactant molecules have both hydrophobic and hydrophilic moieties, which affect the fibers' surface wettability [24]. The results suggested that emulsion electrospinning could be utilized as a general approach for tailoring the hydrophilicity of nanofiber mats, particularly for hydrophobic polymers.

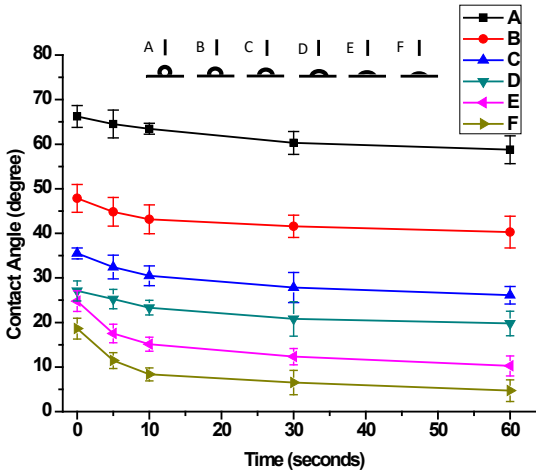


**Figure 3.** Water contact angle of PVA/POX-Span-80 composite nanofibers at ratios of PVA/POX of 5/5 (A), 6/4 (B), 7/3 (C), 8/2 (D), 9/1 (E), and 10/0 (F) as-spun

**Table 2.** A comparison of the water contact angles between emulsion nanofibers and non-emulsion nanofibers with various PVA/POX ratios

| Sample of PVA/POX | Water contact angles of emulsion nanofibers (°) | Water contact angles of non -emulsion nanofibers (°) |
|---|---|---|
| 10/0 | 18.62 | 24.08 |
| 9/1 | 24.77 | 30.14 |
| 8/2 | 27.08 | 35.52 |
| 7/3 | 35.50 | 40.97 |
| 6/4 | 47.85 | 52.84 |
| 5/5 | 66.22 | 65.31 |

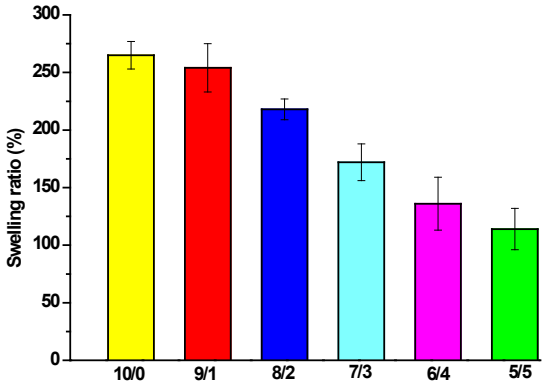


**Figure 4.** Swelling ratio of PVA/POX-Span-80 composite nanofibers at various ratios

## 3.3 Release and morphological sustainability

The *in vitro* release profile of Rhodamine B from PVA/POX-Span-80 composite nanofibers in phosphate buffer solution (pH~7.4) was investigated to determine whether the composite nanofiber mats electrospun from the emulsion could serve as drug encapsulation and release vehicles. Figure 5a shows the release profiles of Rhodamine B-loaded PVA/POX-Span-80 composite nanofibers for the time interval of 360 min. The release rate of the nanofibers with a PVA/POX-Span-80 ratio of 10/0 was found to be the highest. Then, the release rate decreased as the POX content increased. The results indicate that POX can be used to adjust the rate of drug release in the PVA-based composite nanofiber system. Note that the drug release behavior of Rhodamine B-loaded PVA/POX-Span-80 composite nanofibers was in line with the results obtained from the studies of water contact angle and swelling ratio. When the water contact angles were compared, as-spun 10/0 nanofibers appeared to be more hydrophilic than the other composite nanofibers, and thus the as-spun 10/0 nanofibers exhibited a higher permeability to surrounding PBS, allowing Rhodamine B molecules to diffuse rapidly through the as-spun 10/0 nanofibers. The lowest hydrophilicity of the nanofibers with a PVA/POX-Span-80 ratio of 5/5 can be linked to their lowest release rate. The solubility of this prepared nanofiber may be the lowest because of its high hydrophobicity.

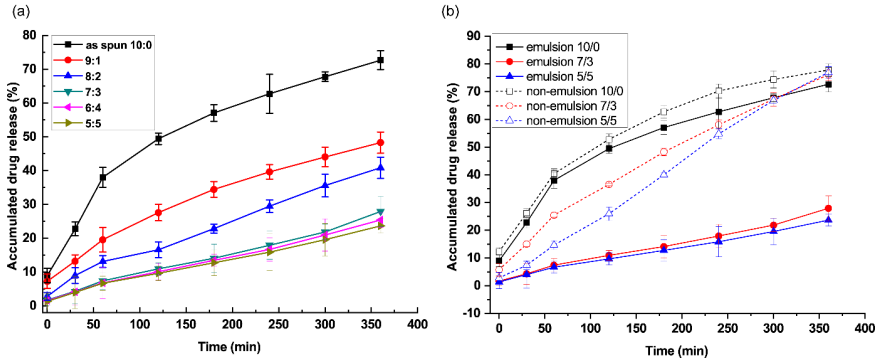


**Figure 5.** (a) The release profiles of Rhodamine B from the PVA/POX-Span-80 composite nanofibers in PBS at 37 ºC. (b) Comparison of Rhodamine B release profile from the emulsion and non-emulsion PVA/POX composite nanofibers in PBS at 37ºC.

The release behavior of emulsion nanofibers (Rhodamine B, PVA, POX, and Span-80) and non-emulsion nanofibers (Rhodamine B, PVA, and POX) was studied. The release rates of emulsion composite nanofibers and non-emulsion composite nanofibers with different PVA/POX ratios (i.e., 10/0, 7/3, and 5/5) showed a different release profile, as shown in Figure 5b. Emulsion nanofibers were shown to have a lower release rate than non-emulsion nanofibers. The difference in release rates between emulsion and non-emulsion nanofibers was noticeable in the nanofiber with a PVA/POX ratio of 5/5, as shown in Table 3. When the POX and Rhodamine B were wrapped in Span-80, the use of Span-80 to form an emulsion solution may have resulted in a reduced release of emulsion nanofibers. Furthermore, Span-80 can improve the stability of polymeric emulsion nanofibers by crosslinking polymer chains via intermolecular interactions [24].

According to the results in Figure 5b, a drug's release time can be split into two stages: the first stage was from 0 to 60 min, and the second stage was from 60 to 360 min. The release rates in these two stages for all nanofibers are summarized in Table 3. The release rate of the first stage was higher than the second stage for all nanofibers except for the 5/5 ratio. The initial release of drugs in the first stage would be associated with the rapid desorption and diffusion of drugs entrapped at the surface of the nanofibers. At the second stage, drug diffusion occurred from the matrix's inside and the process was linked to POX degradation. We found that adding POX delayed the release rate of nanofibers (in both emulsions and non-emulsions). In comparison to PVA, POX had greater water stability due to its hydrophobic properties [19]. As a result, the solubility of PVA/POX nanofibers with high POX and low PVA content (e.g., 5/5) was slower than that of nanofibers with low POX and high PVA content (e.g., 7/3). As a result, high release rates in the first stage were therefore observed in the nanofibers with low POX content and high PVA content. In the second stage, the release rate of nanofibers with high POX content was higher than that of nanofibers with high PVA content. Typically, drug release from matrix polymeric nanofibers occurs as follows: diffusion through the polymer matrix, polymer degradation, and drug desorption from the nanoporous surface of the nanofibers [25, 26]. In our case, the higher release rate observed in the second stage for the nanofibers with PVA/POX ratios of 5/5 was likely due to the Rhodamine B being mainly entrapped inside the POX. At this stage, the POX started to degrade, and Rhodamine B could then be released from the matrix nanofibers. It was important to note that the release behavior of PVA-based polymeric nanofibers could be effectively controlled by adjusting their added POX content and adding Span-80.

**Table 3.** The release profiles of Rhodamine B from the emulsion and non-emulsion of PVA/POX electrospun nanofibers in PBS at 37ºC

| **Sample of PVA/ POX** | **Release Rate (mg% /min)** | | | |
|---|---|---|---|---|
| | **First Stage (0-60 min)** | | **Second Stage (61-360 min)** | |
| | **Non-emulsion** | **Emulsion** | **Non-emulsion** | **Emulsion** |
| 10/0 as spun | 0.469 | 0.483 | 0.123 | 0.056 |
| 9/1 | 0.429 | 0.204 | 0.124 | 0.062 |
| 8/2 | 0.38 | 0.172 | 0.15 | 0.068 |
| 7/3 | 0.328 | 0.095 | 0.169 | 0.092 |
| 6/4 | 0.289 | 0.086 | 0.202 | 0.095 |
| 5/5 | 0.198 | 0.088 | 0.214 | 0.115 |

Figure 6 reveals the morphologies of the emulsion nanofibers and non-emulsion nanofibers after 24 h of immersion in PBS (pH~7.4). As shown in Figures 6a, c, and e, the morphologies of emulsion nanofibers remained as fibers. The non-emulsion nanofibers, in contrast to emulsion nanofibers, disintegrated following immersion in PBS; the nanofiber structure could not be seen, as illustrated in Figures 6b, d, and f. Nanofibers containing Span-80 (an emulsion) were more stable than non-emulsion nanofibers. This could be because the Span-80 in the emulsion nanofibers could promote intermolecular interactions via hydrogen bonding and/or hydrophobic interactions [16]. As a result, the low release rate observed in emulsion nanofibers could be explained by the fibers' excellent stability. Thus, the drug release rate was able to be adjusted by enhancing the matrix's stability.

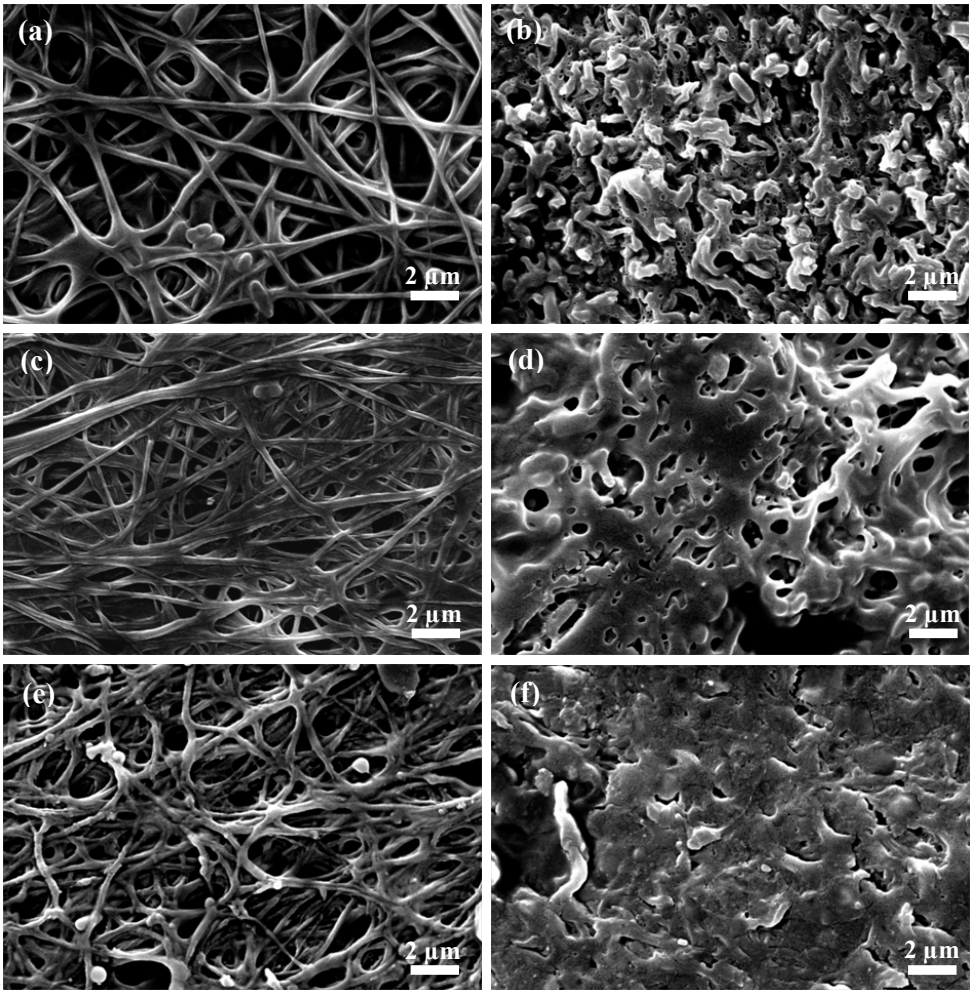


**Figure 6.** SEM images showing representative morphologies of PVA/POX composite nanofibers at various ratios from emulsion (a, c, e) and non-emulsion (b, d, f) electrospinning: (a, b) 10/0, (c, d) 7/3, and (e, f) 5/5 after immersion in PBS (pH~7.4) for 24 h.

## 4. Conclusions

PVA/POX-Span-80 composite nanofibers with varying PVA/POX ratios were fabricated via emulsion electrospinning. Rhodamine B was encapsulated into the PVA/POX-Span-80 nanofibers. According to the results, Span-80 could be used to extend the Rhodamine B release and improve the aqueous medium integrity of the nanofibers. Additionally, increasing the POX content had a substantial effect on the release of encapsulated Rhodamine B. Rhodamine B was released from emulsion PVA/POX-Span-80 composite nanofibers in two stages, each stage controlled by polymer degradation mechanisms. The PVA/POX ratio dictated Rhodamine B release, with the rate of release decreasing as the POX content in the nanofibers increased. These approaches have the potential to be used as platforms for controlled drug delivery.

## 5. Acknowledgements

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