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Preparation of chitosan-based nanofiber nonwoven mats containing Soluplus® as a potential polymeric carrier by electrospinning process

Pembuatan anyaman nirtenun serat nano berbasis kitosan yang mengandung Soluplus® sebagai polimer pembawa potensial dengan proses electrospinning

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ABSTRACT

A preparation of chitosan-based nanofiber nonwoven mats loaded with Soluplus as a novel carrier polymer was carried out. Soluplus, a water-soluble amphiphilic copolymer, was added to provide a nanofiber structure that will be useful in applications as drug delivery system. In this study, a mixture of chitosan, polyethylene oxide (PEO), and Soluplus micelles was electrospun into nanofibers and characterized using SEM to observe the fiber morphology. Rhodamine (Rh) was used as a model molecule trapped inside Soluplus micelles. The results showed that chitosan-based nanofiber nonwoven mats were successfully realized by electrospinning of the chitosan/PEO polymer blend solution at a ratio of 3:2 with 4 wt% total polymer concentration. The optimum electrospinning parameters to obtain the nanofibers were at 30 kV electrical potential, 0.2 ml/hour feed rate, and 30 cm distance between the needle tip and the collector. The addition of Soluplus at four times greater critical micelles concentration (CMC) was still able to provide smooth and bead-less nanofibers morphology. Nanofiber nonwoven mats with Rh-Soluplus have an average fiber diameter of 56 nm, a slightly thinner than the nanofibers with chitosan/PEO alone (63 nm). A preliminary study of Rh release from Soluplus micelles, as well as from Soluplus loaded in the nanofiber mats, showed slower release of Rh from Soluplus loaded in the nanofiber mats compared to the free Soluplus.

Kata kunci:
kitosan;
electrospinning;
nanofibers;
polietilen oksida (PEO);
Soluplus®

ABSTRAK

Telah dilakukan pembuatan anyaman nirtenun serat nano berbasis kitosan yang mengandung Soluplus sebagai polimer pembawa yang baru. Soluplus, sebagai kopolimer ampifilik yang dapat larut dalam air, ditambahkan untuk menyediakan struktur serat nano yang akan berguna pada aplikasi sistem penghantaran obat. Pada penelitian ini, campuran misel kitosan, polietilen oksida (PEO), dan Soluplus dipintal secara elektrik menjadi serat nano dan dikarakterisasi menggunakan SEM untuk mengamati morfologi serat. Rhodamine (Rh) digunakan sebagai molekul model yang terperangkap di dalam misel Soluplus. Hasil penelitian menunjukkan bahwa anyaman nirtenun serat nano berbasis kitosan dapat terbentuk dengan pemintalan elektrik pada rasio campuran kitosan/PEO 3:2 dengan total konsentrasi polimer 4% berat. Parameter pemintalan elektrik yang optimum digunakan untuk memperoleh serat nano, yakni pada tegangan listrik 30 kV, laju alir 0.2 ml/jam, dan jarak antara ujung jarum spineret dan kolektor 30 cm. Penambahan Soluplus pada konsentrasi misel kritis (CMC) 4 kali lebih besar masih mampu menghasilkan morfologi serat nano yang halus dan tanpa butiran. Anyaman nirtenun serat nano dengan Rh-Soluplus memiliki diameter serat rata-rata 56 nm, sedikit lebih tipis dari serat nano dengan kitosan/PEO saja (63 nm). Studi awal pelepasan Rh dari misel Soluplus dan dari Soluplus yang dimuat dalam anyaman serat nano, menunjukkan bahwa pelepasan Rh dari Soluplus yang dimuat dalam serat nano lebih lambat dibandingkan dari Soluplus bebas.

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1. Introduction

A method to develop nanofiber-based drug delivery systems for poorly soluble drugs is proposed by mixing a chitosan-based polymer blend with Soluplus, a commercial water-soluble copolymer (produced by BASF, pharmaceutical grade). Soluplus is a graft copolymer of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol with an amphiphilic chemical structure (Figure 1). Thanks to its dual character, it is able to act as a polymer matrix for forming a solid solution and also as an active solubilizer of many poorly soluble drugs in aqueous media (lipophilic drugs) (Bhuptani et al., 2016; Nagy et al., 2012). Soluplus can increase the bioavailability of this drug, thus potentially enlarge its application in pharmaceuticals. It can be applied either in capsule and tablet formulation or sprayed onto the drug-free pellets to get drug layering pellet (BASF, 2010). A study has also investigated its promising utilization as a drug delivery system to overcome multidrug resistance in cancer treatment (Jin, Zhou, Xue, & San, 2015). A recent study has also reported another novel application of Soluplus as the only polymer carrier in electrospun polymeric nanofibers loaded with poorly water-soluble drug (piroxicam) and designed for wound healing and burn therapy (Paaver et al., 2014).

Besides improving the solubility of poorly water-soluble drugs, the amphiphilic character of Soluplus can be beneficial as the surfactant for electrospinning process. The effect of surfactants addition to the chitosan blended polymer solution has been investigated in some previous studies, resulting in the alteration of surface tension, conductivity of the solution, as well as modulation of the polymer-polymer interactions (Kriegel, Kit, McClements, & Weiss, 2009; Ziani et al., 2011). Due to these alterations, it induces spinnability and affects the fiber morphologies, i.e., needle-like, smooth, or beaded nanofibers (Kriegel et al., 2009). On top of that, it was reported that the presence of surfactants above their critical micellar concentration (CMC) brings more significant functionality to the nanofiber. This is in accordance with previous information that the micellar structure of surfactant can act as carriers for lipophilic components, such as pharmaceuticals and antimicrobials (Jalvandi et al., 2017; Kriegel et al., 2009). Based on the previous studies, Soluplus has a potential to be applied as a surfactant to facilitate the electrospinning process of chitosan nanofibers.

This study aims to realize the electrospun chitosan nanofibers with the presence of Soluplus as a carrier polymer of poorly water-soluble drugs. A preliminary study of Soluplus performance as a novel and promising polymer carrier to control the release of a hydrophobic molecule was also investigated in this study. To improve the electrospinnability and morphological characteristics as well as the functionality of chitosan-based nanofibers, PEO was added to the polymer matrix according to the parameters optimized in a prior study (Yulina, Winiati, Bonadies, Laurienzo, & Dal Poggetto, 2018). Soluplus micelles loaded with rhodamine (Rh) as a model molecule were obtained by nanoprecipitation method.

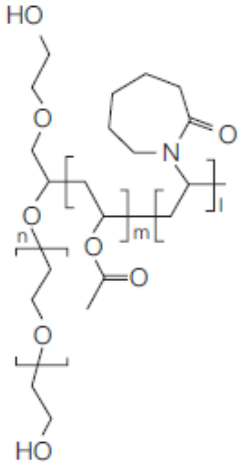

Figure 1. Soluplus graft copolymer chemical structure (Charernsriwilaiwat, Rojanarata, Ngawhirunpat, Sukma, & Opanasopit, 2013)

These Rh-Soluplus micelles were then incorporated into the chitosan/PEO solution at a given concentration. Rh was used as a model due to the easy method of quantitative determination by UV Vis spectroscopy. The optimum electrospinning conditions were determined by observing the polymer jet during the process and the nanofiber morphology obtained, preferably homogeneous and less-beaded nanofiber imaged by Scanning Electron Microscopy (SEM). A preliminary study of Rh release profile from the chitosan-based nanofibrous matrix was also carried out by comparing the Rh release profiles of the nanofibers loaded with free Rh with the nanofibers carrying Rh-loaded Soluplus micelles.

All nanofibers were characterized using SEM. The micelles properties, i.e., size, polydispersity index (PDI), and zeta potential, were analyzed using Dynamic Light Scattering (DLS). The Rh release profiles were analyzed using UV Vis spectroscopy.

2. Method

2.1. Materials

Low molecular weight chitosan powder (50-190 kDa, degree of deacetylation 75-85%), polyethylene oxide (PEO, 900 kDa), Rhodamine B (Rh), and dialysis bag with molecular weight cut-off 2 kDa were supplied by Sigma Aldrich. Acetic acid glacial (purity 99-100%) was obtained from Chem-Lab. Soluplus® was kindly supplied by BASF, The Chemical Company.

2.2. Preparation of blank and Rh loaded micelles (Rh-Soluplus)

Blank and Rh loaded micelles (Rh-Soluplus) were prepared according to the nanoprecipitation method. To prepare the blank micelles, 10 mg Soluplus® was dissolved in 1 ml acetone and then added dropwise to 4 ml distilled water under stirring at 500 rpm. The stirring was continued at room temperature for about 5 hours until complete acetone evaporation. Subsequently, the blank micelles solution was freeze-dried under vacuum

at -80°C for 8 hours to remove water. The nanoparticles obtained from freeze-drying were then re-dispersed in 4 ml of distilled water for characterization.

Preparation of Rh-Soluplus was done following the same procedure as the blank micelles. 0.2 mg rhodamine (Rh) was first dissolved together with 10 mg Soluplus in 1 ml acetone (2 wt% Rh in Soluplus micelles). The solution was then added dropwise to 4 ml distilled water (Rh and Soluplus ratio was 1:50 (w/w). The Rh-Soluplus solution was freeze-dried at -80°C for 8 hours after removing acetone by evaporation. Afterward, the freeze-dried Rh-Soluplus was re-dispersed in 4 ml distilled water. The dispersed solution can later be added to the chitosan/PEO solution at various concentrations for the preparation of micelles-loaded nanofibers by electrospinning process.

2.3. Characterization of blank and Rh-Soluplus micelles

Both blank micelles and Rh-loaded micelles were characterized for size using Dynamic Light Scattering (DLS) (Zetasizer Nano Z, Malvern Instruments Ltd). The zeta potential of blank micelles, Rh-Soluplus micelles, and Rh Soluplus micelles dispersed in the chitosan/PEO solution was also measured using nanosizer. This last measurement aimed to evaluate the stability of micelles nanoparticles in the polymer solution.

2.4. Electrospinning of chitosan/PEO solutions containing free Rh-Soluplus

4 wt% chitosan/PEO at ratio 3:2 (which presented the best nanofiber morphology from the previous study) (Yulina et al., 2018) was chosen for electrospinning with an encapsulated model drug. For this reason, the Rh-Soluplus suspension was added to the chitosan/PEO solution at 30.4 mg/L Soluplus concentration (4 times CMC) and 0.608 mg/L Rh concentration (2 wt% Rh in Soluplus micelles). As the control, 4 wt% chitosan/PEO 3:2 solution was also prepared for electrospinning. To study the influence of Soluplus as polymer carrier, 4 wt% chitosan/PEO 3:2 solution containing free Rh at the same concentration (0.608 mg/L) was also electrospun. The same optimized electrospinning parameters were applied to all chitosan/PEO solutions, i.e., 30 kV electrical potential, 0.2 ml/hr feed rate, and 30 cm distance from needle to the collector. 4 ml of each polymer solution were electrospun and the nanofibers were collected on the aluminum foil.

2.5. Release tests from Rh-Soluplus micelles and nanofibers loaded with Rh-Soluplus

For the Rh release test from Soluplus micelles, 15 mg of freeze-dried Rh-Soluplus was dispersed in 30 ml phosphate buffer saline (PBS) solution and placed inside a dialysis bag. A solution of free Rh in water containing the same Rh amount (3.33 mg/L) was also prepared. The dialysis bag was then immersed into a beaker containing 70 ml of PBS. The release was followed at 37°C under slow stirring. At predetermined time points, 1 ml of the release medium was withdrawn, and the concentration of Rh was determined by measuring the absorbance at 553 nm by UV Vis spectroscopy. After the measurement, the sample was put back into the beaker.

Rh release profiles from both nanofibers (with and without Soluplus) were also investigated. Due to the very limited amount of Rh loaded in nanofibers (which is only 0.608 mg/L as previously mentioned), the drug release test of nanofibers was carried out with a slightly different procedure. The collected nanofiber was entirely detached from the aluminum foil, weighed, and then placed in a small dialysis tube. 3 ml of PBS medium were added into the tube and then immersed in a larger beaker containing 7 ml PBS medium. The release study was also performed at 37°C under slow stirring. Similar to the previous release test, 1 ml of release medium was withdrawn at scheduled times, analyzed by UV Vis, and then put back into the beaker. 1 ml of the release medium was withdrawn, and the concentration of Rh was determined by measuring the absorbance at 553 nm by UV Vis spectroscopy. After the measurement, the sample was put back into the beaker.

3. Result and discussion

3.1. Characterization of blank Soluplus micelles and Rh-Soluplus micelles

Both blank Soluplus micelles and Rh-Soluplus micelles were characterized. The formation of micelles was observed by particle size analyzer. The effect of freeze-drying and successive re-dispersion of micelles in water was also analyzed. As presented in Table 1A, the particle size of blank Soluplus micelles in water rise from 67 to 81 nm, with the increase of Soluplus concentration from 7.6 to 625 mg/L. The unimodal size distribution appeared with polydispersity index (PDI) is above 0.2. Instead, the size of freeze-dried Soluplus micelles at concentrations ranging from 625 to 1250 mg/L, as presented in Table 1B, was nearly constant (around 65-66 nm), as expected, with unimodal and narrower size distribution (PDI values are below 0.2). It means that freeze-drying process indeed can help to preserve the micelles nanoparticles from aggregation at higher Soluplus concentration, which is a good indication for increasing the Soluplus concentration to encapsulate more drugs inside nanofibers without affecting the size of the micelles.

The loading of Rh to Soluplus micelles also did not change the size and distribution of the micelles significantly after the freeze-drying process and re-dispersion in water. It is confirmed by the mean particle size of re-dispersed Rh-Soluplus micelles (at 30.4 mg/L Soluplus concentration), which was 67.61 nm with shallow PDI value of 0.04. The range size of these micelles and their unimodal distribution are in a good agreement with previous study using Soluplus micelles to load Lornoxicam as a drug (Bhuptani et al., 2016). The size of the micelles after re-dispersion in water was still retained even after 17 days (average size was 63.86 nm). It means that freeze-dried micelles dispersion in water is stable over a long period of storage.

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Table 1.
Mean particle size and polydispersity index of Soluplus micelles at different concentrations (7.6 mg/L corresponds to Soluplus CMC in water)

Micelles concentration (mg/L)	Mean particle size (nm)	Polydispersity Index (PDI)
A. Soluplus micelles as prepared		
7.6	67.55	0.222
15.2	69.43	0.254
625	81.05	0.250
1250	73.80	0.146
B. Soluplus micelles after freeze-drying and water re-dispersion		
625	65.68	0.178
833	66.55	0.156
1250	65.35	0.191

Table 2.
Zeta potential values of Soluplus freeze-dried nanoparticles re-dispersed in different solutions at 625 mg/L concentration (n = 3)

Soluplus micelles in different formulations	Zeta potential (mV)	Mean particle size (nm)	Polydispersity index (PDI)
H_2O	-8.83 ± 0.17	65.7 ± 0.5	0.18 ± 0.03
50% acetic acid	14.62 ± 0.20	124.9 ± 1.3	0.07 ± 0.03
Chitosan/PEO 3:2 in 50% acetic acid solution	48.8 ± 2.94	n.a.*	n.a.*

**Mean particle size and PDI of micelles in chitosan/PEO polymer solution were not reliable, due to the presence of aggregation phenomena between the polymer chains*

The size of both blank and loaded micelles is essential since they will be encapsulated within the chitosan/PEO nanofibers. It was expected that the Rh-loaded micelles have a good range of size so that it is possible to encapsulate them nicely inside the nanofibers and avoid the formation of beaded nanofibers, as reported in a previous study by Yang et al. (Yang, Wang, Li, Ding, & Zhou, 2014). However, in 50% acetic acid aqueous solution, which is the solvent for both chitosan and PEO polymers, larger micelles with the average size of 124.9 nm and 130 nm formed at Soluplus concentration of 625 and 1250 mg/L, respectively. This result may be attributed to the formation of larger micelles or their aggregation.

The zeta potential accounts for formation of more stable micelles when the Soluplus nanoparticles were re-dispersed in acid solution. As can be seen in Table 2, Soluplus micelles that were re-dispersed in water have a low negative zeta potential value (-8,83 mV) indicative of the incipient instability of micelles. However, when it was re-dispersed in 50% acetic acid, the zeta potential was increased to 14.62 mV and became positive.

Furthermore, it is noticeable from Table 2 that the zeta potential value of micelles in the presence of chitosan/PEO is even much higher than zeta potential in acetic acid. Taking into account that chitosan nanoparticles have a positive zeta potential (Chang, Lin, Wu, & Tsai, 2015), this result could be an indication of the absorption of chitosan/PEO polymers onto nanoparticles surface, thus forming an external chitosan layer. The establishment of interactions between polymers and micelles is promising for the obtainment of a good micelles dispersion inside the final nanofibers.

3.2. SEM images of freeze-dried Rh-loaded micelles and chitosan/PEO nanofibers

To see the morphology of freeze-dried Rh-Soluplus micelles, SEM analysis was performed. Figure 2 shows that at two different high magnifications, spherical-like morphology are visible. However, the size of micelles observed by SEM is not significant since micelles in water are hydrated. Therefore, the micelles size measurement still relies on the DLS analysis. This spherical morphology of Rh-loaded micelles is in accordance with the reported TEM image results of doxorubicin and furosemide-loaded Soluplus micelles (Alopaeus, Hagesæther, & Tho, 2019; Jin et al., 2015).

As previously discussed, the optimum polymer solution for the best nanofiber morphology was 4 wt% total polymer concentration of chitosan/PEO at a ratio of 3:2 (Yulina et al., 2018). Additionally, the optimum solution electrospinning parameters were fixed at 30 kV electrical potential, 0.2 ml/h polymer feed rate, and at 30 cm distance between the tip of the needle and the collector. For a preliminary study of Rh release, two nanofiber mats were fabricated applying the same electrospinning parameters and using 4 ml polymer solution of chitosan/PEO 3:2 loaded with free Rh and chitosan/PEO 3:2 loaded with Rh-Soluplus at 4 times CMC (30.4 mg/L of Soluplus concentration). The SEM images of these electrospun nanofibers were depicted in Figure 3 and Figure 4, respectively.

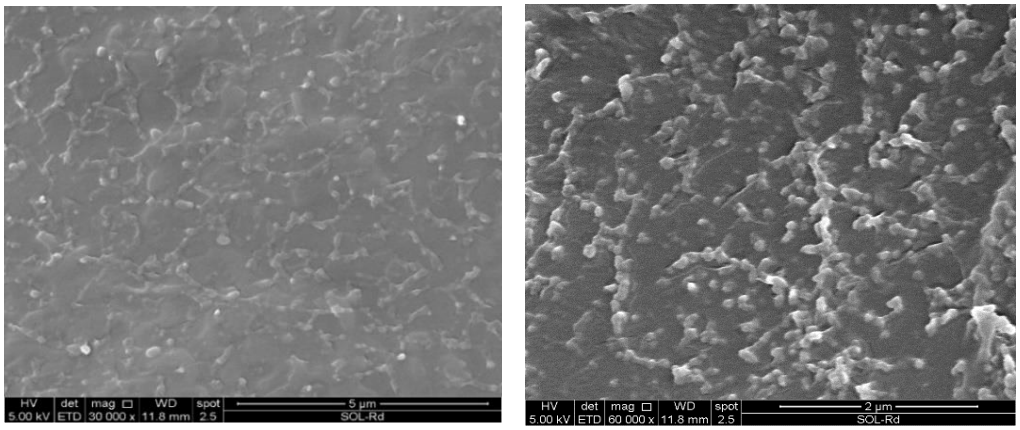
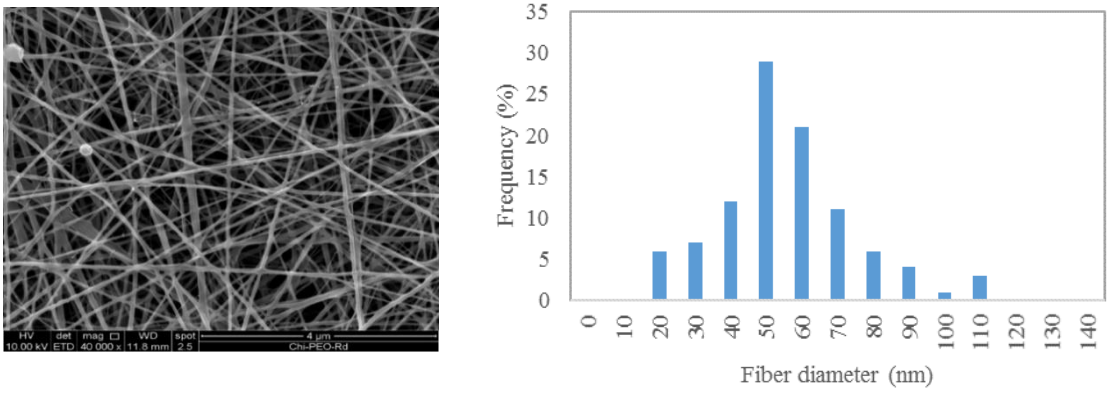
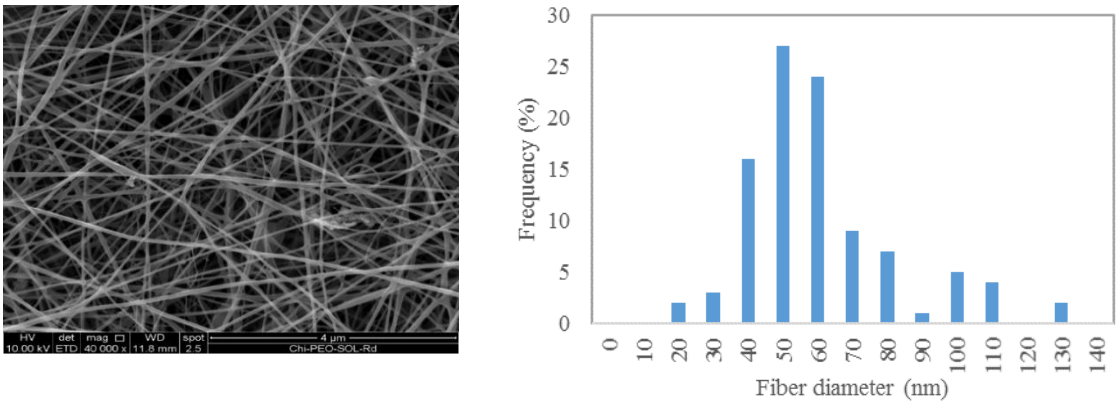


Figure 2. SEM images of freeze-dried Rh-Soluplus micelles at different magnification



(a) (b)

Figure 3. SEM image (a) and size distributions (b) of 4 wt% chitosan/PEO 3:2 electrospun nanofibers loaded with Rh



(a) (b)

Figure 4. SEM image (a) and size distribution (b) of 4 wt% chitosan/PEO 3:2 electrospun nanofibers with Rh-loaded Soluplus

Representative SEM images in Figure 3 and Figure 4 both showed a similarly uniform and fewer beads nanofibers morphology, with the most fibers size ranging from 50-60 nm. The average diameters of nanofibers loaded with Rh and Rh-loaded Soluplus were 51 and 56 nm, respectively. The differences in fiber size distributions of both mats seem to be insignificant according to the fiber size distribution profiles (Figure 3 and 4).

From the SEM images, it seems that the aggregation of Soluplus nanoparticles observed in acetic acid solution, as previously discussed, did not occur. The micelles were encapsulated within the nanofibers, since nanofibers appear regular and uniform also after inclusion of Rh-Soluplus micelles. The dimension of particles after the solvent evaporation is supposed to be lower with respect to hydrated micelles, hence they can be confined within the fibers. It would be necessary to increase the fiber

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diameter and enhance the mechanical strength of the electrospun nanofibers to fulfill the application requirements in biomedical field, such as wound dressing mats for skin wound healing. In fact, nanofibers fabricated by electrospinning has drawn a lot of attention recently, especially for application in wound healing. This is due to the material's capability for mimicking the extracellular matrix (ECM) composition of skin tissue from various types of natural and synthetic polymers (Chen et al., 2017). To meet this functionality, chitosan has been electrospun with a wide range of polymers such as polycaprolactone (PCL), collagen, PVA, and PEO with incorporation of various substances as a healing agent (Ahmadi Majd, Rabbani Khorasgani, Moshtaghian, Talebi, & Khezri, 2016; Charernsriwilaiwat et al., 2013; Chen et al., 2017; Wang, Cheng, Gao, & Wang, 2015). These studies revealed that the mean diameter of nanofibers is around 200-350 nm, which is higher than chitosan/PEO nanofibers fabricated in this study.

3.3. Preliminary Rh release test

To know the role of Soluplus micelles in the release of Rh, a study was conducted using the dialysis bag immersed in PBS. The solution with free Rh in water was also prepared as a blank. From the preliminary observation, the release of Rh in both conditions was very slow. Only after two days, Rh content in the released medium could be detected. The observation at the 3rd day of release is presented in Table 3.

Table 3
Release test of Rh after 3 days (72 hours) incubation from UV Vis measurement at 553 nm wavelength

Solutions	Initial Rh concentration (mg/L)	Rh concentration after 3 days* (mg/L)
Free Rh	3.33	0.71
Rh-Soluplus	3.33	0.38

**measured in the release medium*

According to this preliminary study, as expected, Rh concentration is lower when it is encapsulated within the Soluplus micelles, confirming the ability of micelles to act as a delivery system. However, to ensure the Soluplus role in the drug delivery behavior, a more comprehensive release test over a longer time is required.

Following the collection of electrospun nanofibers, the model-drug release test of all nanofibers was also performed. Taking into account that 2 wt% of Rh is encapsulated within Soluplus nanoparticles (assuming a 100% encapsulation efficiency) and Soluplus concentration in polymer solution corresponds to 4 times CMC (30.4 mg/L), before the electrospinning process, free Rh was added to the chitosan/PEO solution at the same theoretical amount. Both samples were prepared to compare the release of free Rh from nanofibers and the release of Rh encapsulated in Soluplus from nanofibers.

After the consecutive 30 min, 60 min, 1 hr, 2 hr, and even one day, no Rh was found in the medium by UV analysis from both nanofibers samples. However, at a visual inspection, inside the dialysis membrane tube, the PBS medium in which nanofibers with free Rh were placed showed a bit pink color due to Rh after 2 hours. The changing color of the medium after 2 hours indicates that free Rh was easier to be released from the nanofiber compared to Rh-Soluplus within the nanofibers. In the first case, the free Rh can be released as soon as the fibers were swollen in the medium. Instead, in the other case, the release of Rh encapsulated in Soluplus within the nanofibers did not occur even after a period of one day. Afterward, a more sustained release of Rh from micelles is expected to occur. This preliminary observation shows that Soluplus can potentially act as a carrier for controlled release of Rh from the nanofibers.

This behavior is similar to other results reported in literature. Chitosan-EDTA/PVA nanofibers system showed a rapid release of lysozyme (LZ) approximately 80% within 30 minutes and then the release was slowly increased to 90% in 4 hours (Charernsriwilaiwat, Opanasopit, Rojanarata, & Ngawhirunpat, 2012). Another study with the same nanofibers system revealed the release of *Garcinia mangostana* extracts, which reaches approximately 80% within 60 minutes and then also showed a slower increased to 90% in 8 hours (Charernsriwilaiwat et al., 2013). Both release profiles indicate a burst release of the substances at the initial step, which can be explained by polymer swelling and erosion as well as the diffusion of the substances (Alopaeus et al., 2019; Charernsriwilaiwat et al., 2013). According to those studies, the use of Soluplus as the carrier could be an option to be used for a particular wound healing system that needs to prevent burst release of the drug at the initial step.

4. Conclusion

Smooth and beadless nanofibers were successfully obtained by electrospinning of chitosan/PEO polymer solution with a total concentration of 4 wt%, a ratio of 3:2, and addition of Soluplus under 30 kV electrical potential. The feed rate was 0.2 ml/hr and the distance between the needle tip and the collector was 30 cm. The higher chitosan ratio in the nanofibers is favorable for its antibacterial property. Soluplus addition to the solution of chitosan/PEO at a ratio 3:2 and concentration higher than its critical micelles concentration (CMC) has no significant effect on the nanofiber morphology according to the SEM images.

The Soluplus characterization with DLS showed a larger micelles size when it dispersed in 50% acetic acid than in water, with an average size of 124.9 nm and 130

nm at Soluplus concentration 625 and 1250 mg/L respectively, due to micelles aggregation. However, the smooth, thin, and beadless electrospun nanofibers were still achieved with the addition of Soluplus to the polymer solution. The average diameter of chitosan/PEO nanofibers alone was 63 nm, while chitosan/PEO nanofibers loaded with free rhodamine and rhodamine-loaded Soluplus had a slightly thinner average fiber diameter (51 and 56 nm, respectively). According to the results, Soluplus can be potentially used as a drug carrier in chitosan nanofibers. An increasing diameter of nanofibers followed by a more comprehensive release test is a necessary goal to be achieved in order to find suitable applications in the biomedical field, such as wound dressing mats for skin wound healing.

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References

Ahmadi Majd, S., Rabbani Khorasgani, M., Moshtaghian, S. J., Talebi, A., & Khezri, M., 2016. Application of Chitosan/PVA nano fiber as a potential wound dressing for streptozotocin-induced diabetic rats. *International Journal of Biological Macromolecules*, *92*, 1162–1168. https://doi.org/10.1016/j.ijbiomac.2016.06.035

Alopaeus, J. F., Hagesæther, E., & Tho, I., 2019. Micellisation mechanism and behaviour of Soluplus® – furosemide micelles : preformulation studies of an oral nanocarrier-based system, (Figure 1), 1–23. https://doi.org/10.3390/ph12010015

BASF., 2010. Soluplus - Technical Information. *BASF Group - Pharma Ingredients & Services*.

Bhuptani, R. S., Jain, A. S., Makhija, D. T., Jagtap, A. G., Rahiman Hassan, P. A., & Nagarsenker, M. S., 2016. Soluplus based polymeric micelles and mixed micelles of lornoxicam: Design, characterization and In vivo efficacy studies in rats. *Indian Journal of Pharmaceutical Education and Research*, *50*(2), 277–286. https://doi.org/10.5530/ijper.50.2.8

Chang, S. H., Lin, H. T. V., Wu, G. J., & Tsai, G. J., 2015. pH Effects on solubility, zeta potential, and correlation between antibacterial activity and molecular weight of chitosan. *Carbohydrate Polymers*, *134*, 74–81. https://doi.org/10.1016/j.carbpol.2015.07.072

Charernsriwilaiwat, N., Opanasopit, P., Rojanarata, T., & Ngawhirunpat, T., 2012. Lysozyme-loaded, electrospun chitosan-based nanofiber mats for wound healing. *International Journal of Pharmaceutics*, *427*(2), 379–384. https://doi.org/10.1016/j.ijpharm.2012.02.010

Charernsriwilaiwat, N., Rojanarata, T., Ngawhirunpat, T., Sukma, M., & Opanasopit, P., 2013. Electrospun chitosan-based nanofiber mats loaded with Garcinia mangostana extracts. *International Journal of Pharmaceutics*, *452*(1–2), 333–343. https://doi.org/10.1016/j.ijpharm.2013.05.012

Chen, S., Liu, B., Carlson, M. A., Gombart, A. F., Reilly, D. A., & Xie, J., 2017. Recent advances in electrospun nanofibers for wound healing. *Nanomedicine*, *12*(11), 1335–1352. https://doi.org/10.2217/nnm-2017-0017

Jalvandi, J., White, M., Gao, Y., Truong, Y. B., Padhye, R., & Kyratzis, I. L., 2017. Polyvinyl alcohol composite nanofibres containing conjugated levofloxacin-chitosan for controlled drug release. *Materials Science and Engineering C*, *73*(December), 440–446. https://doi.org/10.1016/j.msec.2016.12.112

Jin, X., Zhou, B., Xue, L., & San, W., 2015. Soluplus® micelles as a potential drug delivery system for reversal of resistant tumor. *Biomedicine and Pharmacotherapy*, *69*, 388–395. https://doi.org/10.1016/j.biopha.2014.12.028

Kriegel, C., Kit, K. M., McClements, D. J., & Weiss, J., 2009. Electrospinning of chitosan-poly(ethylene oxide) blend nanofibers in the presence of micellar surfactant solutions. *Polymer*, *50*(1), 189–200. https://doi.org/10.1016/j.polymer.2008.09.041

Nagy, Z. K., Balogh, A., Vajna, B., Farkas, A., Patyi, G., Kramarics, A., & Marosi, G., 2012. Comparison of electrospun and extruded Soluplus®-based solid dosage forms of improved dissolution. *Journal of Pharmaceutical Sciences*, *101*(7), 2271–2280. https://doi.org/10.1002/jps.22731

Paaver, U., Tamm, I., Laidmäe, I., Lust, A., Kirsimäe, K., Veski, P., … Heinämäki, J., 2014. Soluplus graft copolymer: Potential novel carrier polymer in electrospinning of nanofibrous drug delivery systems for wound therapy. *BioMed Research International*, *2014*, 14–18. https://doi.org/10.1155/2014/789765

Wang, X., Cheng, F., Gao, J., & Wang, L., 2015. Antibacterial wound dressing from chitosan/polyethylene oxide nanofibers mats embedded with silver nanoparticles. *Journal of Biomaterials Applications*, *29*(8), 1086–1095. https://doi.org/10.1177/0885328214554665

Yang, G., Wang, J., Li, L., Ding, S., & Zhou, S., 2014. Electrospun micelles/drug-loaded nanofibers for time-programmed multi-agent release. *Macromolecular Bioscience*, *14*(7), 965–976. https://doi.org/10.1002/mabi.201300575

Yulina, R., Winiati, W., Bonadies, I., Laurienzo, P., & Dal Poggetto, G., 2018. Optimization of solution condition and electrospinning process parameters for synthesis of chitosan-PEO nanofibers. *Arena Tekstil*, *33*(1), 1–10. https://doi.org/http://dx.doi.org/10.31266/at.v33i1.3537

Ziani, K., Henrist, C., Jérôme, C., Aqil, A., Maté, J. I., & Cloots, R., 2011. Effect of nonionic surfactant and acidity on chitosan nanofibers with different molecular weights. *Carbohydrate Polymers*, *83*(2), 470–476. https://doi.org/10.1016/j.carbpol.2010.08.002