Selective pH-Responsive Core—Sheath Nanofiber Membranes for Chem/Bio/Med Applications: Targeted Delivery of Functional Molecules

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Supporting Information

ABSTRACT: Core-sheath fibers using different Eudragit materials were successfully produced, and their controlled multi-pH responses have been demonstrated. Core-sheath fibers made of Eudragit L 100 (EL100) core and Eudragit S 100 (ES100) sheath provide protection and/or controlled release of core material at pH 6 by adjusting the sheath thickness (controlled by the flow rate of source polymer solution). The thickest sheath (~250 nm) provides the least core release

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~1.25%/h, while the thinnest sheath (~140 nm) provides much quicker release ~16.75%/h. Furthermore, switching core and sheath material dramatically altered the pH response. Core—sheath fibers made of ES100 core and EL100 sheath can provide a consistent core release rate, while the sheath release rate becomes higher as the sheath layer becomes thinner. For example, the thinnest sheath (~120 nm) provides a core and sheath release ratio of 1:2.5, while the thickest sheath (~200 nm) shows only a ratio of 1:1.7. All core—sheath Eudragit fibers show no noticeable release at pH 5, while they are completely dissolved at pH 7. Extremely high surface area in the porous network of the fiber membranes provides much faster (>30 times) response to external pH changes as compared to that of equivalent cast films.

KEYWORDS: coaxial electrospinning, core-sheath nanofibers, multi-pH-responsive, Eudragit, target delivery, nanofiber membrane

INTRODUCTION

Systemic drug delivery has been the most commonly used method to treat many diseases, but its efficiency is limited. Because the drug is delivered to the entire body, its concentration is diluted by bloodstream distribution, resulting in reduced efficacy and possible side effects, especially in chemotherapy treatments for cancers. Local molecule delivery targeted to specific organs can take advantage of different pH levels present in the targeted organs.¹ A pH-sensitive dissolution can be utilized to locally deliver the anticancer drug, either treating cancers or preventing the recurrence of cancers after surgery. Another important application field is the detection of chemical and biological (chem/bio) agents causing pH changes in the local environment, such as bacteria² and organophosphates.^{3,4}

Eudragit polymers are widely used as active pharmaceutical ingredients in drug capsules and tablets.^{5,6} Until the 1950s, orally administered medication could not control the release time and location. Eudragit, developed by Röhm & Haas GmbH in Darmstadt Germany, solved this major problem of the oral medications by developing pH-sensitive polymers based on functionalization of methacrylic acids. The first commercial Eudragit product introduced in 1953 was soluble in basic conditions, so that it can protect active ingredients in the very acidic condition of the stomach.⁷ Since then, Eudragit polymers based and the stomach.⁷ Since then and the stomage of the stomage of

been extensively used in the development of oral drugs, which can release drugs in targeted organs, such as stomach (pH 1– 5), duodenum (pH > 5.5), jejunum (pH 6–7), and ileum (pH > 7). In 1968, Eudragit polymers insoluble at any pH level were developed to provide controlled release over many hours.

Table 1 lists several types of Eudragit polymers and their dissolving pH ranges. Eudragit L 100 (EL100) and Eudragit S 100 (ES100) are anionic copolymers derived from methacrylic acid and methyl methacrylate, designed to dissolve in neutral or alkaline fluids. The ratios of the free carboxyl groups to the ester groups are ~1:1 and 1:2 in EL100 and ES100, respectively. Eudragit E 100 is a cationic copolymer derived from dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate with 2:1:1 composition, designed to dissolve in acidic fluids. The chemical structures of several Eudragit polymers are shown in Figures S1a and S1b. Figure S1c shows the pH values found in several inner organs of the human body.

Various methods for delivering Eudragit polymers have been used: ionic complexation,⁹ in situ emulsification,¹⁰ wet granulation method followed by enteric coating,¹¹ solvent casting method,¹² direct compression,¹³ etc. The electro-

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Name	Solubility	Solvents						
		Alcohols	Dichloromethane	Ethyl acetate	1N NaOH	Water		
Eudragit E 100	Gastric fluid to pH 5	Soluble	Soluble	Soluble	-	Insoluble		
Eudragit L 100	Intestinal fluid from pH 6	Soluble	Insoluble	Insoluble	Soluble	Insoluble		
Eudragit L 100-55	Intestinal fluid from pH 5.5	Soluble	Insoluble	Insoluble	Soluble	Insoluble		
Eudragit S 100	Intestinal fluid from pH 7	Soluble	Insoluble	Insoluble	Soluble	Insoluble		
Eudragit RL 100	High permeability	Soluble	Soluble	Soluble	-	Insoluble		
Eudragit RS 100	Low permeability	Soluble	Soluble	Soluble	-	Insoluble		
L100-55 soluble in duodenum								



spinning technique has been established as a versatile method for producing nanofiber membranes made of many natural and/or synthetic materials, including biomaterials,^{14–16} textile polymers,^{17,18} electrically conducting polymers,^{19,20} and stimuli-responsive polymers.^{21–23} By adjusting solution properties and electrospinning conditions, one can control the following: (a) fiber diameter, ranging from micro- to nanometer dimensions; (b) fiber composition; (c) fiber morphology (e.g., smooth, wrinkled,^{24,25} porous,^{26,27} beaded,^{28,29} etc.); (d) fiber structure, either monolithic, side-by-side,^{30,31} core– sheath,^{32,33} or coaxially trilayered.^{34,35} Electrospun membranes have a porous nonwoven mat configuration, providing exceptionally high surface-area-to-volume ratio and excellent breathability, enabling fast response to external stimuli, such as pH, light, etc.

The versatility of electrospinning can be greatly expanded by coaxial electrospinning that provides the production of coresheath structured fiber in a single step. This approach enables the combination of multiple functions into one fiber. In addition, by dissolving or dispersing functional molecules into each polymer solution, one can selectively incorporate functional molecules into either core or sheath layers. Figure 1 shows the diagram of the coaxial electrospinning process and the basic setup. For coaxial electrospinning, two syringe pumps are used to feed a coaxially structured nozzle. The inner and outer nozzles are electrically connected, and therefore, the electric potential is applied to the overall nozzle. Core and sheath solutions are separately fed through the coaxial nozzle. Each syringe pump provides constant and continuous flow with its own rate precisely. Triaxial electrospun fibers (core/ intermediate/sheath) can be formed to provide additional functionalities from the intermediate layer and/or to prevent undesired interference between the core and the sheath layer.

Previously, we have reported the effect of operational electrospinning parameters (e.g., flow rate ratio, solvent selection, nozzle dimensions, etc.) on the membrane release



Figure 1. Diagram of coaxial electrospinning and resulting core-sheath fibers.

rate of incorporated model drugs from both fiber core and sheath. 35

As shown in Table 1, each type of Eudragit polymer is dissolved in a certain pH range depending on its chemical composition. Very recently, nanostructured Eudragit polymers have emerged that can provide an extremely sensitive pH response with a faster dissolution rate than in bulk form. Recent reports using electrospun Eudragit fibers have demonstrated versatile properties compared with other types of nanostructures such as micro/nanoparticles. Shen et al. first demonstrated³⁶ Eudragit L 100-55 nanofiber membranes incorporated with diclofenac sodium using electrospinning in 2011, which provide the pH-dependent release of the incorporated drug. The same group also demonstrated core-sheath fibers using PVP sheath and Eudragit L100-55 core in 2013,³⁷ and Eudragit S100 sheath and composite drug core in 2016.³⁸ In 2015, Illangakoon et al. reported³⁹ core-sheath fibers using Eudragit S100 as a sheath material to encapsulate the 5-fluorouracil (5-FU) anticancer drug loaded core. However, although ES100 is not soluble in pH 1.0, significant release of core material was observed because of the low molecular weight of 5-FU drug.

More recently, novel muco-adhesive nanofiber membranes for oral mucosal drug delivery were developed using PVP/Eudragit RS100 mixture by Santocildes-Romero et al.⁴⁰ All previously reported Eudragit fibers provide only a *single* pH response using one Eudragit polymer. However, response to multiple pH conditions from one substrate will be a very important asset for various applications. Liu et al. demonstrated multistate pHresponsive composite particles using microfluidic approaches, providing two-stage dissolution at pH 6.0 and pH 6.5 for advanced drug delivery applications. Krogsgaard et al. also demonstrated⁴¹ a bistable gel system using multi-pH-responsive self-healing hydrogels, which provide different mechanical properties depending on pH level.

Here, we report on novel multi-pH-responsive Eudragit nanofiber membranes using two different Eudragit polymers, as illustrated in Figure 2. EL100 polymer is dissolved at pH 6 or



Figure 2. Cross-sectional diagrams of Eudragit core–sheath fibers made of (a) EL100 core and ES100 sheath or (b) ES100 core and EL100 sheath, and their evolution in consecutive pH changes.

higher, while ES100 polymer is dissolved at pH 7 or higher. With the combination of these two Eudragit polymers into different lavers (either in core or sheath) of core-sheath fibers, different dissolution and release kinetics at different pH environments can be obtained. For core-sheath fibers made of EL100 core and ES100 sheath (Figure 2a), because both Eudragit polymers are not dissolved at pH 5, no release of Eudragit and incorporated material is observed. At pH 6 the EL100 core is dissolved, and core material is released in a sustained manner due to the protection from ES100 sheath layer. At pH 7, the ES100 sheath and the remaining EL100 core with incorporated molecules will be completely dissolved and released. When the material combination is switched between core and sheath, very different pH responses are observed, as illustrated in Figure 2b. As expected no release is shown at pH 5. At pH 6, the EL100 sheath is released, followed by ES100 core release at pH 7. Many combined multi-pH responses can be obtained by selecting appropriate Eudragit polymers for core and sheath.

EXPERIMENTAL SECTION

Materials. All Eudragit polymers including Eudragit L 100 and S 100 were generously provided by Evonik Corporation (Parsippany, NJ). Ethanol (200 proof, ACS grade) and dimethylacetamide (DMAc, extra pure 99.5%) solvents were purchased from Fisher Scientific (Hampton, NH). Since dual responses from core and sheath need to be characterized simultaneously, Keyacid Blue (KAB) and Keyacid Uranine (KAU) dyes purchased from Keystone Inc. (Chicago, IL)

were used as dissolution indicators because their optical absorption peaks do not overlap, which enables the simultaneous measurement of the corresponding release kinetics using UV–vis spectroscopy. All materials and solvents were utilized as received without any modification.

Electrospinning. Two solutions were prepared for coaxial electrospinning. The mixture of ethanol and DMAc in 7:3 weight ratio was used as a solvent. Eudragit L 100 solution was prepared by dissolving EL100 into the solvent mixture and then adding KAB dye. For Eudragit S 100 solution, KAU dye was dissolved first, and then ES100 was added into the solution, because KAU dye cannot be dissolved well once ES100 is dissolved. Whenever any material was added to the solution, the mixture was stirred overnight using a rotating agitator at 20 rpm to obtain homogenized solutions. Once solutions were prepared, each solution was loaded into the syringe pump connected to either the core or sheath nozzle opening. Syringe pumps deliver the solutions at constant flow rates to the nozzle. High voltage applied between the nozzle and conducting substrate ejects the liquid jet from the nozzle. The ejected jet experiences stretching and whipping actions within the gap distance of 20 cm between nozzle and substrate, while evaporating the solvent thoroughly. Solidified electrospun nanofiber membranes were obtained at the substrate. For comparison purposes, all membranes were prepared from the same set of solutions with fixed polymer-to-dye ratio. The total volume of electrospun core solution was fixed to incorporate the same amount of dyes into the core. All electrospinning conditions are summarized in Table S1.

pH-Triggered Dissolution Test. To quantify the dissolution of Eudragit, we incorporated different indicating dyes into the core and the sheath. Optical absorption spectra were obtained using a PerkinElmer UV–vis spectrometer. Prepared membrane samples were placed into Petri dishes, which contained 40 mL of colorless pH buffer solution. Each set of measurements was carried out at predetermined times after sample placement. A 1 mL portion of solution was taken from the Petri dish into the UV-transparent cuvette to measure the absorption spectrum, and then the measured sample solution was restored to the Petri dish after the measurement. To confirm consistency of results, we repeated the experiment three times using three different samples.

RESULTS AND DISCUSSION

Our experimental results have demonstrated the concept of novel membranes/textiles that can provide different responses to multiple pH conditions. Coaxially electrospun fiber mats using two different pH-responsive polymers, such as Eudragit S 100 and L 100 polymers, were successfully obtained. The fibers consist of multiple layers, each of which can have their own pH range for triggered dissolution. Our core—sheath fiber membranes, using commercially available Eudragit polymers, provide multi-pH responses within physiological pH ranges.

Production of Electrospun Fibers Using Eudragit Polymers. Single (homogeneous) electrospinning and coaxial (core-sheath) electrospinning using different Eudragit polymers have been carried out, and respective fiber morphologies were obtained, as shown in Figure 3. EL100 (Figure 3a) and ES100 (Figure 3b) provide sufficient viscosity and electrical conditions in solution to produce uniform fibers during electrospinning. For Eudragit E 100 (EE100), electrosprayed microparticles (Figure 3c) were produced even with 20 wt % concentration in the solution due to the low solution viscosity. Coaxial electrospinning either with EL100 core and ES100 sheath or with ES100 core and EL100 sheath polymers were successful and produced uniform fiber membranes, as shown in Figure 3d-i. Different flow rates for core and sheath were used during coaxial electrospinning to manipulate both core diameter and sheath thickness in order to evaluate the effect of fiber geometry on dissolution and release kinetics under



Figure 3. SEM images of (a) EL100 electrospun fibers; (b) ES100 electrospun fibers; (c) EE100 electrosprayed particles; and coresheath fibers made of EL100 core and ES100 sheath using respective flow rates (mL/h) of (d) 0.4 and 1.3, (e) 0.4 and 0.8, (f) 0.4 and 0.4. (g-i) Core-sheath fibers made of ES100 core and EL100 sheath using the same set of flow rates.

various pH conditions. Considering the fiber diameter, polymer concentration, density of solutions, and flow rates, estimated core diameter and the sheath thickness are obtained as summarized in Tables S1 and S2. Although various flow rates were used, resulting fiber diameters are very similar for the same material set of electrospinning core and sheath solutions. This is because the higher electric field was used for higher total (core + sheath) flow rates, leading to more vigorous whipping and stretching actions during electrospinning. Interestingly, EL100 core and ES100 sheath fibers (Figure 3d–f) have noticeably larger fiber diameters than ES100 core and EL100 sheath (Figure 3g–i) as listed in Table S1. Switching core and sheath solutions can alter the fiber morphologies and diameters because of different surface properties of the liquid jet during the electrospinning processes.

TEM was investigated as a means to observe the core—sheath structure of core—sheath fibers. Eudragit L100 and S100 polymers are chemically and physically very similar copolymers derived from methacrylic acid and methyl methacrylate with different ratios, there is only a minimal density difference ($\sim 0.01 \text{ g/cm}^3$) between the two materials. As a result, it was not possible to obtain a clear core—sheath structure definition through TEM observation.

Different pH Responses of Homogeneous Electrospun Eudragit Fibers. Using homogeneous EL100 fibers, simple pH-responsive dissolution tests have been carried out to observe the pH-dependent dissolution behavior, as shown in Figure 4.

Buffer solutions of pH 4 and pH 7 were used, and for comparison, different types of samples, such as cast film and electrospun membranes, were prepared using the same amount (100 μ L) of EL100 polymer solution. Surprisingly, extremely quick total dissolution (<10 min) was observed at pH 7, while no dissolution occurred at pH 4 even after 1 week. Moreover, when the EL100 fiber membrane was fully dissolved at pH 7, no sign of dissolution was observed for the EL100 cast film. Full dissolution of EL100 cast film required ~5 h, which is >30 times slower than that of electrospun fiber membranes. From this test, we can conclude that electrospun Eudragit fibers are extremely sensitive to the pH environment. Apparently,



Figure 4. pH-triggered dissolution of Eudragit L100 electrospun fiber membranes and cast film. A 100 μ L portion of EL100 20 wt % solution was used for all samples.

extremely high surface area from the highly porous network of nanofibers enables quick and sensitive response to external conditions.

These pH-dependent dissolution rates were quantitatively analyzed by measuring absorption spectra of released materials in ambient solution, with the results shown in Figure 5.

For detection of the dissolution of Eudragit fiber membranes, Keyacid Blue (KAB) dye was added to the Eudragit solution, which was used to produce KAB-incorporated electrospun Eudragit fiber membranes. Figure 5a,b shows the dissolution profile of EL100 and ES100 fiber membranes, respectively. Complete dissolution of EL100 fiber membranes was observed for both pH 7 (<30 min) and pH 6 (<2.5 h), as shown in Figure 5a. No dissolution was observed for pH 4 and pH 5. For ES100 fiber membranes, dissolution only occurred at pH 7 (Figure 5b). Because pH 7 is the *lowest* pH condition of ES100 dissolution, complete dissolution requires a relatively longer time than EL100 fibers at pH 7, but it is expected to be much quicker at pH 8 or higher solutions. Interestingly, slight release was observed for EL100 fibers at pH 4 and pH 5. Considering the insolubility of EL100 in these pH conditions, it is probably caused by overloading with KAB dye. For ES100 fibers, abundant ester groups provide higher loading and binding capacity for the incorporated dyes. Photos of Eudragit fiber membranes in these pH solutions are shown in Figure S2. In contrast to electrospun nanofiber membranes, cast films of EL100 and ES100 were dissolved very slowly and required up to 6 days for total dissolution (Figure 5c).

Multi-pH Responses of Core–Sheath Eudragit Fibers. Multi-pH responses from core–sheath Eudragit fibers are demonstrated in Figure 6. Two different dyes were used to evaluate the dissolution of core and sheath layers separately. By varying core and sheath flows rates, we evaluated the effect of sheath thickness on the pH response kinetics.

At pH 5, no release occurred (Figure 6a,b) for either core or sheath, as expected. At pH 6, the core dissolution/release was dramatically varied by adjusting the flow rate ratio between core and sheath, as shown in Figure 6c. For the thinnest sheath (0.4 and 0.4 mL/h) case, most of the core was released (as indicated by saturation of accumulated release) very quickly within 4 h, while the core was released in a highly sustained manner from the thickest sheath (0.4 and 1.3 mL/h) case. Moderate sheath thickness provides intermediate release kinetics between the thin and thick sheath cases. Slight releases from the sheath layers, although supposedly not soluble at pH 6, were observed with similar trends as compared to the core release (Figure 6d).



Figure 5. Quantitative analysis of Eudragit electrospun fiber mats in different pH conditions: (a) Eudragit L 100 fibers; (b) Eudragit S 100 fibers; and (c) Eudragit L 100 cast film at pH 6 and Eudragit S 100 cast film at pH 7.



Figure 6. Response of core-sheath Eudragit membranes in different pH conditions: (a) core release at pH 5; (b) sheath release at pH 5; (c) core release at pH 6; (d) sheath release at pH 6; (e) core release at pH 7; and (e) sheath release at pH 7. Photographs of membranes after (g) 1 min and (h) 4 h in different pH solutions.

This is possibly due to the interdiffusion between core and sheath layers. Even with slight interdiffusion, it can affect the release kinetics of both layers. Further improvement can be obtained with the addition of an intermediate layer between core and sheath using triaxial electrospinning. At pH 7, both core and sheath materials are completely released within 4 h, as shown in Figure 6e,f, respectively. The images shown in Figure 6g,h clearly show the different dissolution/release behaviors in different pH conditions. After 4 h, no color change and complete dissolution of membranes were observed in solutions



Figure 7. Selective pH responses to consecutively changing pH conditions using core–sheath fibers: EL100 core and ES100 sheath with different flow rates (mL/h) of (a) 0.4 and 1.3, (b) 0.4 and 0.8, and (c) 0.4 and 0.4 vs core–sheath fibers made of ES100 core and EL100 sheath with different flow rates of (d) 0.4 and 1.3, (e) 0.4 and 0.8, and (f) 0.4 and 0.4. (n = 3, error bar represents the range between maximum and minimum values among tests.)

at pH 5 and pH 7, respectively. Some release (mostly from core with KAB dye) was observed at pH 6 while still maintaining membrane integrity. A potential application of these pHresponsive Eudragit fibers is localized cancer therapy. Because cancer cells provide a slightly acidic environment (pH ~6.5),⁴² we have also evaluated the fiber membrane response behavior at pH 6.5 as shown in Figure S3. As expected, the sheath layer was not dissolved at pH 6.5, even though it is very close to its dissolution point of pH 7. On the other hand, the core was dissolved/released with different rates depending on the sheath thickness. It is noted that the release rates are faster than that of pH 6.0 (Figure 6c) because the dissolution speed of Eudragit L100 core becomes faster at higher pH environment.

We have also applied the core-sheath Eudragit fiber membrane to the condition where the pH changes with time. This is very important from a practical point of view because the pH-responsive system will go through different pH conditions consecutively in most situations. Core-sheath fibers made of EL100 core and ES100 sheath and its reverse combination were produced, and their multi-pH responses are shown in Figure 7, with the pH changing consecutively from pH 5 to pH 7.

For the EL100 core and ES100 sheath fibers (Figure 7a–c), as expected no release was observed at pH 5 for 2 h, followed by exposure to pH 6 solution resulting in significant release from the core and weak or moderate sustained release from the sheath. When the membrane was next exposed to pH 7 solution it released all sheath material and remaining core

material and was completely dissolved. Interestingly, coresheath fibers with thicker sheath wall (higher sheath solution flow rate) provide more sustained release than those with thinner sheath wall. Figure 7a has the thickest sheath wall, and there is almost no release in pH 6 for 2 h. This protection behavior was caused by a sufficiently thick ES100 sheath layer. The thinner sheath wall in Figure 7b shows well-sustained release (~15% for 2 h) of core material, while the thinnest sheath wall (Figure 7c) provides faster core release (\sim 70% for 2 h). Clearly, the dissolution rate of core material can be controlled by adjusting sheath thickness, which is determined by the flow rate ratio between core and sheath solutions. For core-sheath fibers made of ES100 core and EL100 sheath, very different dissolution characteristics are observed as shown in Figure 7d-f. Weak release and complete dissolution were observed at pH 5 and pH 7, respectively. At pH 6, different release kinetics were observed depending on sheath thickness. In contrast to the core-sheath fibers with EL100 core and ES100 sheath, thinner sheath provides more distinctive release differences between core and sheath. With the thickest sheath (Figure 7d), 26% of core material and 45% of sheath material were released at 6 h. However, with the thinnest sheath (Figure 7f), 28% of core material and 71% of sheath material were released. For moderate sheath thickness (Figure 7e), 31% of core and 61% of sheath were released. The release ratio between core and sheath materials was varied from 1:1.7 to 1:2.5.

CONCLUSION

We have demonstrated membranes of core—sheath fibers using two different Eudragit polymers leading to multi-pH responses within the physiological pH range. This successful demonstration will open up new areas of applied research in multiaxial electrospinning, a promising research area for applications ranging from biomedical to sensor applications. Many different multi-pH responses can be obtained using different Eudragit polymer combinations. The knowledge gained from this report can be used to produce new multi-stimuli-responsive materials with active components for advanced drugs and sensors for targeted disease and toxic molecules, which can also provide real-time sensing of various threats. Real-time sensing capabilities and quick membrane response can provide precious time to respond appropriately to ever changing conditions in the field.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsami.7b16080.

Chemical structures, summaries of electrospinning parameters and fiber dimensions, photos of fiber membranes, and accumulated release vs time (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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