ABSTRACT

MANASCO, JOSHUA LEE. Functional Nanofibers via Electrospinning: New Materials and Processes. (Under the direction of Prof. Saad A. Khan).

Cyclodextrins are fascinating, amphiphilic molecules that are of considerable interest due to their ability to be used in a variety of applications ranging from pharmaceuticals and cosmetics to foods and agriculture. These are ring-shaped sugar molecules possess a hydrophobic cavity and a hydrophilic exterior which imparts them water solubility. There are three main types of naturally occurring cyclodextrins namely α-, β- and γ-CD which have 6, 7 and 8 member rings, respectively. Owing to their hydrophobic interior, cyclodextrin molecules encapsulate hydrophobic guest molecules (from small to macromolecules) to form host-guest supermolecular structures. Chemically modified CDs are often preferred to the natural forms, particularly methylated (MβCD) and hydroxypropylated (HPβCD) cyclodextrins, for their enhanced solubility and chemical stability.

Electrostatic spinning (electrospinning) of nanofibers has drawn significant research attention in recent decades. This technique involves the stretching of a polymer solution or melt in a high electric field to produce fibers on the nanoscale. These 1-Dimensional nanostructures possess extraordinary surface-to-weight ratio and find applications that vary from filtration membranes and tissue scaffolding materials to drug delivery and many others.

The scope of this research attempts to leverage the unique features of CDs with the high aspect ratio of nanofibers to create functional nanomaterials. The present study can be divided into three sections. In the first part, we establish that CDs can be electrospun without the need for a “carrier” polymer. This discovery may serve to extend the horizon of what is
currently considered “electrospinnable” from macromolecules now to small molecules. The ability to electrospin CDs led to their incorporation of other polymers to create bicomponent fibers with poly (vinyl alcohol) (PVA) and polyacrylonitrile (PAN). In the case of PVA we demonstrate the ability to not only to control the fiber properties based on PVA/CD ratio, but also crosslink these fibers to create water resistant fiber mats. Furthermore, the use of these fibers as rapid dissolving membranes for drug delivery is explored. Additionally, CDs are investigated for use as a porogen for PAN and carbon fibers. We find that CDs are particularly good candidates for us as porogens due to their amorphous nature and versatility to be dissolved in various solvent system.

By nature, solution electrospinning is a low-throughput, solvent intensive process. In the last part we attempt to alleviate this issue by designing an extrusion based melt electrospinning device. We show that submicron fibers of polycaprolactone are possible through this technique without the use of organic solvents.
Functional Nanofibers via Electospinning: New Materials and Processes

by
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A dissertation submitted to the Graduate Faculty of North Carolina State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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Biography

Joshua Manasco was born on July 12, 1981 in Tryon, NC to his parents Robert and Rebecca Manasco. After graduating high school, he stayed close to home and attended Midlands Technical College to study General Engineering. After two years of attendance, he enrolled at the University of South Carolina (USC) to pursue Chemical Engineering. Upon completion of his Bachelor’s degree in 2004, Josh joined the PhD program in Chemical Engineering at North Carolina State University. His dissertation research was guided by Prof. Saad Khan. In June of 2010, Josh joined Zeus Industrial Products Inc. in Orangeburg, SC.
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I am grateful to Dr. George Roberts who is no longer with us. He was one of my favorite teachers and personalities, he will be missed dearly. Additionally, I would like to thank Dr. Benham Pourdeyhimi for serving on my dissertation committee. A special thanks to my substitute committee members, Dr. Michael Dickey and Dr. Orlando Rojas, for accepting the positions at a moment’s notice. I would like to acknowledge the National Science Foundation Science and Technology Center (NSF-STC) for providing financial aid for this work.

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CHAPTER 1

Motivation, Goals and Organization
1.1 Motivation and Goals

The overarching objectives of this study are to i) create functional fibers by including cyclodextrins as a component in nanofibers, and ii) extend the scope of what is considered “electrospinnable” from small molecules to polymer melts.

One-dimensional (1-D) nanostructures such as nanofibers and nanorods have attracted much attention as of late due to their extraordinary properties and novel applications\textsuperscript{1, 2}. While there have been many techniques developed for fabricating these 1-D nanostructures, electrostatic spinning (electrospinning) appears to be the simplest and most versatile technique for creating these nanostructures, primarily nanofibers, from a variety of polymers and composites\textsuperscript{1-4}. Conventional textile fiber technologies aimed at producing microdenier fibers (0.2-1.5 denier per filament) often involve complicated, multi-step techniques that may not always be practical, cost-effective, or easily functionalizable\textsuperscript{1}. Additional techniques such as fiber drawing, template synthesis, phase separation and self-assembly can create small samples of polymer nanofibers at the lab scale, however these techniques are not considered commercially scalable\textsuperscript{2}. Other advantages of the electrospinning technique are the ability to control fiber diameter, high aspect ratio, and the unique pore size of the non-woven fabric produced. Additionally, composites can be easily produced with the only caveat being that the composite materials are either finely dispersed or readily soluble in the polymer/solvent system chosen. The ability to produce 1-D nanomaterials via electrospinning provides a facile, scalable technique that finds applications in sensors, electronic devices\textsuperscript{5, 6}, catalysis\textsuperscript{7}, biomedical devices\textsuperscript{8-11} and filtration\textsuperscript{12-18}.
Electrospinning requires a very simple setup: a viscous solution or melt; a high voltage power supply, an electrode (usually a capillary or needle tip), and a grounded or oppositely charged collector. Electrospinning makes use of charges that are applied to a fluid to provide a stretching force to a collector where there is a potential gradient. When a sufficiently high voltage is applied, a polymer liquid jet erupts from a polymer solution drop. The key stages of electrospinning, as described by Reneker et al., are: launching of the jet; elongation of a straight segment; development of whipping instability; and solidification of the jet into a solid fiber. Electrospinning is a variation of electrospraying, and has been studied extensively over the past couple of decades. The main difference between the two processes is driven by chain entanglements involved in the spinning solutions. The result of these entanglements is the extraction of a fiber instead of a droplet formed during electrospraying from the explosion of the supercharged droplet of solution at the terminus of the tip or capillary. The first description of this technique was demonstrated by Formhals in a 1934 patent and a typical laboratory set up is shown in Figure 1.1.

Cyclodextrins, also known as cycloamyloses, were first known in 1891 as cellulosine. Later, Schardinger discovered three naturally occurring cyclodextrins as α-, β- and γ-cyclodextrin, referred to as “Schardinger sugars”, which are structurally 6-, 7-, and 8-membered glucopyranose unit rings respectively. These cyclic structures have been of great interest due to their amphiphilic properties and unusual hosting abilities. The most stable three dimensional structure formed is a truncated cone with a large upper opening formed by secondary hydroxyl groups and a small lower opening formed by primary...
hydroxyl groups creating a hydrophilic outer surface (typical structure shown in Figure 1.2). The presence of glycosidic oxygens inside the toroid creates an electron rich environment resulting in an apolar, hydrophobic cavity allowing them to form host-guest complexes. The stability of these complexes depends on several factors including the size and shape match between host and guest23, 25, 26, chemical environment and the interaction forces between the host CD and guest molecules. While natural CDs are known to complex with a wide variety of molecules, its applications are however restricted by their low water solubility.

It is well-known that CDs self-aggregate in water27-30, and it has been suggested that the limited solubility of natural β-cyclodextrin is due to unfavorable interactions of the aggregates formed in solution with the structure of water30-34. As such, chemical modification of CDs are often undertaken by adding substitutes for hydroxyl groups with even hydrophobic moieties such as methoxy groups to transform α-, β- and γ-CDs from crystalline powders into amorphous mixtures, effectively increasing their solubility31. Two chemically modified β-cyclodextrins of considerable interest for their extraordinary solubilities and ability to complex with a wide range of poorly water soluble species are methyl- (MβCD) and hydroxypropyl- (HPβCD) beta-cyclodextrins. Furthermore, these chemically modified CDs find solubility in a wide range of solvents: water, alcohols, dimethylformamide, dimethylsulfoxide, and formic and acetic acids to name a few. The flexibility in possible solvent systems leads to the ability to incorporate these CDs in a number of polymeric systems.
By leveraging the unique amphiphilic and versatility of CDs with the astonishing aspect ratio of nanomaterials through electrospinning, an exciting group of functional materials may be possible. In creating these unique materials several questions arise:

- Is it possible to electrospin a small molecule such as CD without the need to incorporate a “carrier” polymer to aid in fiber formation?
- What is the effect of incorporating CDs on the solution properties, for both single and bicomponent systems, which influence the electrospinning process and how do they affect the final fiber morphology?
- Can these CDs be used to incorporate a poorly water soluble drug into nanofibers? If so, what are the effects on the addition of a different compatible “carrier” polymer on electrospinnability and drug solubility and release?
- Can we electrospin a bicomponent fiber containing CD and a polymer which phase separates from said CD during the electrospinning process? Can we then remove the CD by means of leaching out or during a carbonization process in which it is pyrolyzed to create a porous fiber structure?

Finally, despite the potential advantages of solution electrospinning, it is a process that is solvent intensive and inherently low throughput because of the constraints imposed by the polymer solution parameters. These drawbacks have prompted efforts to synthesize nanofibers by melt electrospinning. So, we seek to examine if we can develop a scalable process for electrospinning nanofibers from a polymer melt.
1.2 Organization of Dissertation

Although the components and techniques involved with this study have been briefly introduced, each subsequent chapter includes a more detailed discussion related to the background of the specific issues addressed therein. Chapter 2 explores the capability of electrospinning small molecules, in particular chemically modified CDs (HPβCD and MβCD). Additionally, the influence of CD concentration on solution properties is studied in detail. In Chapter 3 a compatible polymer, polyvinyl alcohol (PVA), is added in order to better control fiber formation due to a narrow window for electrospinning CDs alone. We examine the role of each component in electrospinning. More importantly, we show that the PVA-CD system can be crosslinked to produce water insoluble nanofibers which opens the door to future applications for these fibers in an aqueous or humid environment. In Chapter 4 a model, poorly water soluble drug, ketoprofen, is added to the system and the rapid release of fibers containing various ratios of CD to PVA are tested. The CD’s ability to complex with hydrophobic species combined with its extraordinary water solubility provide an opportunity to utilize the high surface area to weight ratio inherent in small fibers in creating a rapid release/dissolution membrane. The utility of CDs to be used as a porogen for polyacrylonitrile (PAN) and carbon fibers is explored in Chapter 5. The ability to distribute a phase separated amorphous domain of small molecules throughout a fiber matrix provides a unique opportunity to create unique micro- and mesoporous materials. Finally, a novel device for electrospinning polymer melts via an extrusion based system is explained in
Chapter 6. Chapter 7 summarizes the key findings of this study and identifies areas for future research.
1.3 References


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Figure 1.1: Typical laboratory setup for electrospinning. This device is similar to the one used throughout this study in Chapters 2-5. Also shown is the formation of a Taylor cone and an as-spun non-woven fiber mat.

Figure 1.2: The (a) chemical and (b) conformational structure of HPβCD.
CHAPTER 2

Cyclodextrin Fibers via Polymer-free Electrospinning

Who needs a polymer? The electrospinning of submicron fibers using a polymer-free system consisting of pure cyclodextrin has been achieved. This work demonstrates for the first time that a non-polymer solution system can be electrospun, thereby belying a commonly accepted belief that only polymers can be electrospun. This discovery not only broadens the gamut of the electrospinning field but also opens up new possibilities for the synthesis of nanoarchitectured supramolecular complexes.
Cyclodextrin Fibers via Polymer-free Electrospinning

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2.1 Introduction

Cyclodextrins (CDs) are intriguing amphiphilic molecules that consist of a hydrophilic outer structure and a hydrophobic core with the ability to act as hosts for both nonpolar and polar guests. Guest entities include macro- and small molecules bound by noncovalent interactions including van der Waals, hydrophobic, hydrogen bonding and electrostatic interactions. Electrospinning is a facile yet effective method for producing nanoscale non-woven mats of fibers, particularly nanofibers with high aspect ratios attractive in diverse applications including membrane technology, reinforced materials, sensors, textiles, tissue engineering and drug delivery. We report for the first time, the fabrication of submicron fibers from highly concentrated hydroxypropyl β-cyclodextrin (HPβCD) by electrospinning without the addition of a carrier polymer. Electrospinning fibers from pure CD would leverage the distinctive properties of these molecules with the unique properties of nanofibers, opening new possibilities for the synthesis of nanoarchitectured supramolecular complexes. This work also demonstrates that a non-polymer solution system can be electrospun belying commonly accepted hypothesis that nanofiber formation by

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electrospinning is only possible with polymers in the presence of adequate chain entanglements. We envisage that non-polymer systems can be electrospun if “pseudo-entanglement” can be achieved through other mechanisms such as aggregation via hydrogen bonding.

CDs are doughnut-shaped cyclic oligosaccharides typically composed of 6, 7 or 8 member α-D-glucopyranose rings (α, β or γ CD, respectively). Native and functionalized CDs are used in various applications because of their ability to encapsulate moieties into their cavities. In pharmaceutics, CDs have been used as complexing agents or additives to aid in drug formulation. Solubility and stability, bioavailability and controlled and sustained delivery of poorly water-soluble insecticides\textsuperscript{23}, dyes\textsuperscript{24, 25} and drugs\textsuperscript{26-35} have been shown to be enhanced in the presence of CDs. CDs have also been used in the stabilization of flavors\textsuperscript{36,37} and fragrances or for the elimination of unwanted tastes, contaminants, and other deleterious compounds in many common consumer products\textsuperscript{1}. In the chemical industry, CDs are used as catalysts for improved selectivity, and for separation and purification of industrial-scale products\textsuperscript{38}.

CD containing nanofibers have been electrospun in multicomponent systems for various applications\textsuperscript{37, 39-49}. The first reported use of CDs employed β-CD as a crosslinking agent to render nanofibers made of poly(acrylic acid) water insoluble\textsuperscript{37}. There are three cases where β-CD was employed in different capacities with poly(vinylpyrrolidone): as a carrier for bicomponent fibers, as a reducing/stabilizing agent for gold nanoparticles, and as a
porogen to create pores in fibers\textsuperscript{39-41}. Recently Uyar \textit{et al.} used $\alpha$-CD to create pseudopolyrotaxanes inclusion complexes with poly(ethylene glycol) and electrospun them using poly(ethylene oxide) as the carrier\textsuperscript{42}. \textit{In each case an electrospinnable polymer is used as a carrier to produce electrospun nanofibers.}

In this study a chemically modified cyclodextrin, HP\(\beta\)CD (Figure 2.1), is electrospun into nonwoven mats of submicron diameter fibers without the addition of a spinnable polymer. Aqueous solutions of HP\(\beta\)CD in a range of 10-80 wt\% were prepared and electrospun.

\textbf{2.2 Experimental Materials and Methods}

HP\(\beta\)CD was purchased from CTD, Inc (High Springs, Fl, technical grade) and used as received. The average degree of substitution for this derivative was 5.6 (computed mol. wt.-1460). M\(\beta\)CD was generously donated by Wacker Chemie (Adrian, Michigan). The average degree of substitution for this derivative was 11.5 (computed mol. wt.-1310). The HP\(\beta\)CD and M\(\beta\)CD solutions were made fresh by adding the respective amounts of CD to de-ionized water, dimethyl formamide (DMF) or formic acid (FA) and allowed to mix in a shaker bath overnight at 35°C. All solutions were stored in a refrigerator when not in use to prevent degradation.

Rheological experiments were performed at 25 °C in a TA Instruments AR-2000 stress rheometer using cone and plate geometry. Measurements were performed at least three
times to ensure reproducibility within ±5%. Bound water studies were done on the HPβCD solutions using a TA instruments® Q2000 Differential Scanning Calorimeter. Each sample (8-12 mg) was loaded into an aluminum hermetic pan and crimped. The samples were ramped from room temperature to 213.15 K and back.

Surface tension measurements at the air/surfactant solution interface were made by the Wilhelmy plate method using a platinum rectangular thin blade. The blade was hooked to a sensitive force transducer. The measured surface tensions of pure water and acetone matched literature values. The electrical conductivity was measured using an EC meter (Fisher Accumet BASIC AB30).

The electrospinning setup consisted of a grounded aluminum collector plate, a precision syringe pump (Harvard Apparatus, Holliston, MA) fitted with metallic needle (22G) syringe, and a high-voltage power supply (Gamma High Voltage Research, model D-ES30 PN/M692 with a positive polarity). The fibers were collected on an aluminum foil wrapped on the collector plate. The tip-to-collector distance and solution flow rate were fixed at 12 cm and 0.5 mL/h, respectively, and the applied voltage ranged between 5 and 11 kV. SEM measurements on gold sputtered fibers were obtained on a Hitachi S-3200 and FEI XL30 scanning electron microscope. The average fiber diameter was determined by measuring 100 individual fibers from multiple SEM images using Revolution SEM™ software (4Pi Analysis, Inc.) and Image J software (NIH). TEM (FEI Tecnai G2 Twin) images were obtained of the nanofibers by directly depositing samples to TEM carbon-coated
copper grids fastened to the aluminum foil and removing them from the collector plate after the electrospinning deposition.

2.3 Results and Discussion

2.3.1 Electrospinning of HPβCD

Representative scanning electron microscopy (SEM) images illustrate a transition from beads to nanofibers (Figure 2.2). For concentrations 50 wt% and lower, electrospraying occurs as only spherical beads are formed (Figure 2.2a). However, at 60 wt% a mix of nanofibers and beads can be seen (Figure 2.2b) as the solution is on the cusp of having enough molecular cohesion to form fibers. At 65 wt% bead defects are absent and only fibers are formed (Figure 2.2c), though these fibers show variability in diameter. This is best explained by an incomplete stretching of the beads present in Figure 2.2b into long spindle-shaped defects combined with a slightly unstable jet produced during spinning. Increasing HPβCD concentration to 70 wt% improves fiber uniformity, as observed in Figure 2.2d. Measurements of fiber diameter are made for each condition and shown in Table 2.1. These results are significant in that it shows that polymer-free electrospun fibers can be achieved for smaller molecules, such as CD. Further, the ability to electrospin at high concentrations creates the opportunity for high fiber yield considering that almost all solution electrospinning is done using low concentration solutions. It should be noted that increasing the concentration of HPβCD beyond 70 wt% renders the solution too viscous for the electrical field to overcome. The surface tension for the solutions plateaus at high
concentrations of HPβCD and remains virtually unchanged above 20 wt%, therefore we do not discuss its effect here when comparing much higher concentrations. The conductivity for the solutions is shown in Figure 2.3. The conductivity of the HPβCD solutions is relatively unchanged at lower concentrations (10-30% (w/w)), after which it declines linearly with concentration. This is due in part to a reduction in the mobility of the bulk water. Similarly, Foster et al. reported a reduction in transport properties (including conductivity) in polymer solutions containing PEO which deviated from ideal due to the hydration of PEO and a decrease in bulk water\textsuperscript{51}. Although, the conductivity changes in the concentration ranges of interest, these solutions are not very conductive, on the order of $\mu$s/s, and the changes are not considered to be as important as the much more significant changes in viscosity. We then surmise that the concentration effects and flow properties of the electrospinning solutions are then of chief importance.

An explanation for being able to electrospin CD solutions is that large aggregates of HPβCD form a pseudo-entangled system allowing for enough molecular cohesion to elongate and form fibers. Although no evidence of aggregation can be seen in low concentrations of HPβCD\textsuperscript{52}, Hausler et al. found a significant rise in viscosity above 50 wt% which they ascribed to self-assembly via hydrogen bonding. We examined the role of hydrogen bonding in CD fiber formation by adding urea, a substance known to disrupt hydrogen bonding\textsuperscript{53}. Figure 2.4 shows that by adding small amount of urea uniform fibers (Fig. 4a) electrospun from 70 wt% HPβCD solution transitions to elongated beaded fibers
(Fig. 2.4b, 10 wt% urea), and finally to a film (Fig. 2.4c, 20 wt% urea). The urea reduces the interactions between the HPβCD molecules in solution causing instability and eventual breakup in the electrospinning jet. The disruption of hydrogen bonding with the addition of urea decreases the viscosity by a factor of eight as shown in Figure 2.5 (which plots the viscosity-shear rate behavior of the 70 wt% HPβCD sample, with and without urea). The HPβCD solution by itself shows Newtonian behavior.

Since our solutions are too concentrated to be examined by microscopy or light scattering, we used rheology and differential scanning calorimetry (DSC) to rationalize further the electrospinnability of HPβCD. The zero-shear viscosity of HPβCD solutions (10-80 wt%) shows a nearly exponential rise with increasing HPβCD concentration which may possibly be due to the aggregates growing in size and interacting via hydrogen bonding.

2.3.2 Concentration effects

To investigate further the role of aggregation, DSC was used to measure the amount of free water present in HPβCD solutions of differing CD concentration. The amount of free water was calculated by measuring the melting energy of ice formed when the frozen solutions were melted and dividing the measured melting energy by the theoretical energy required for melting ice (333.55 J/g). The energy of melting for the different HPβCD solutions was determined from the magnitude of the area of the melting peak (see DSC thermogram in Figure 2.7). For CD concentrations above 50 wt% a dramatic reduction in the amount of free water is observed until almost none exists at 70 wt% HPβCD as the water
molecules are now occupied through hydrogen bonding with CD molecules. This is consistent to what Hausler et al. found in their analysis of free and bound water in concentrated HPβCD solutions. At nearly all the concentrations studied (10-60 wt% HPβCD), a small endothermic peak can be seen at ~260 K which is linked with the liquid crystalline nature of the HPβCD solutions. Above 60 wt% HPβCD, a reduction to almost 0% free water was obtained, indicating a dramatic increase in hydrogen bonding. This substantial increase in hydrogen bonding which is also evidenced by the large increase in viscosity may prevent polymer jet breakup during the electrospinning process, thus facilitating bead-free fiber formation.

Cyclodextrins possess 3 hydroxyl groups (one primary and two secondary) per glucose group for a total of 21 for the beta- species. The primary hydroxyl group is attached to the C-6 carbon on while the secondary hydroxyls are attached to C-2 and C-3 carbons of the repeating glucose groups of cyclodextrins. The structure for beta-cyclodextrin with labeled carbons corresponding to the hydroxyl groups discussed is shown in Figure 2.8.

Shikata et al. studied the hydration and dynamic behavior of various natural and chemically-modified CDs in aqueous solutions. They employed dielectric relaxation measurements to elucidate the relaxation modes involved with water molecules hydrating the CD species. In the study it was determined that the hydration numbers depended strongly on the number of hydroxyl groups and type of modifications. By increasing the 2-hydroxypropoxy or methoxy groups the hydration number increases, and therefore the water
solubility increases over the complementary natural CDs. This is mainly due to a reduction in the side-by-side intramolecular hydrogen bonding present in natural cyclodextrins. The hydration number ($m$) for a HPβCD grade with 22% of its hydroxyl groups substituted (or a degree of substitution = 4.6) with hydroxypropyl groups was found to be approximately $10 \pm 0.3$ (waters/glucose) or $70 \pm 2.0$ (waters/CD).

If we assume that all of the bound water from the calorimetric measurements is hydrating the HPβCD, then we may be able to elucidate the amount of waters of hydration per CD in the aqueous solutions. Figure 2.9 shows how the moles of water per mole of HPβCD vary with concentration. At the lowest concentration studied, 10 wt%, the hydration number, $m = 12.6$, is similar to that found by Shikata. The hydration number then falls dramatically and plateaus at higher concentrations to a value of ~3-5. This is due to interactions between HPβCD as the molecules participate in intermolecular hydrogen bonding with each other instead of water molecules. These findings corroborate our earlier assessment that HPβCD solutions are electrospinnable at higher concentrations because of the robust hydrogen bonded system that is formed between HPβCD molecules. It should be noted that the HPβCD grade studied herein has a higher degree of substitution from the grade studied by Shikata and workers of 5.6 or 26.7% (5.6 substituted/21 total) of its hydroxyl groups are substituted with hydroxypropyl groups, and therefore we do not expect to see exact agreement. Additionally, Shikata studied molar concentrations below 0.1 M, meaning that only our lowest data point is in the range of study, 10 wt% HPβCD (~0.07 M).
Moreover, our data supports their claim that a higher degree of substitution leads to a higher hydration number.

2.3.3 Other Solvents

HPβCD is a versatile molecule as it is not only very soluble in water, but also possesses a high solubility in other polar organic solvents such as dimethylformamide and formic acid. It is expected that if similar concentrations can be achieved in DMF and FA, it may be possible to electrospin fibers from these solvents. SEM micrographs of HPβCD fibers electrospun from solutions of 50 and 60 wt% HPβCD in DMF and FA are shown in Figure 2.10. Only beads were produced in DMF up to 50 wt% HPβCD (Figure 2.10a), however by increasing the concentration further, 60 wt% (Figure 2.10b), continuous fibers were produced. Yet when formic acid is used as the solvent, fibers were achieved at a concentration of 50 (Figure 2.10c) and 60 wt% HPβCD (Figure. 2.10d). To better understand the electrospinnability in these solvents, a summary of fiber statistics and solution parameters is presented in Table 2.2.

The viscosity of the solutions, for the same respective HPβCD concentrations, is relatively similar in magnitude and the surface tensions for the solvents are similar for DMF (40.2 ± 0.3 dynes/cm) and FA (38.5 ± 0.2 dynes/cm). However, there is a large discrepancy seen in the measured values of conductivity, based on the solvent used, owing to the higher dielectric constant and measured electrical conductivity of formic acid employed (51.1 and 350.8 ± 0.5 μS/cm) compared to DMF (38.2 and 2.1 ± 0.2 μS/cm). A drop in conductivity
with increasing HPβCD concentration is seen with these solvents as well and may be attributed to a reduction in the mobility in the system akin to aqueous solutions discussed earlier (Fig 2.3). Additionally, there is a significant difference in the boiling point of these two solvents as FA has a boiling point of ~101 °C while DMF’s boiling point is ~153 °C. Therefore, the differences in electrical conductivity and solvent volatility are viewed as the dominant factors determining morphology and fiber diameter.

As aforementioned, electrospinning involves the transfer of electric charge from electrode to the liquid droplet at the tip. It was found that increasing the conductivity of an electrospinning a polymer solution produced a finer fiber diameter due to the increased stretching that occurs under a high electric field\textsuperscript{55-57}. When comparing fibers electrospun from FA and DMF, the 3-order of magnitude higher electrical conductivity for the FA solutions contributes greatly to the smaller fiber diameters over fibers produced from DMF solutions. Moreover, in electrospinning, as the solution jet is stretched toward the collector, invariably, it’s the evaporation of the solvent from the jet that yields a polymer nanofiber at the collector. Ideally, all traces of the solvent are removed prior to collection of the fibers. However, sometimes incomplete drying, owing to the low volatility of the solvent employed, occurs leading to ribbon-like morphologies due to a fluid-filled fiber impacting the collector causing a collapse and subsequently drying to produce the flattened morphologies seen for the 60% HPβCD/DMF fibers (Figure 2.10b).
In general, a viscous, conductive solution with a low surface tension facilitates the production of defect free nanofibers. It appears that FA may be the best of the three solvents (FA, water and DMF) studied herein for electrospinning HPβCD fibers. Formic acid has the advantage of a lower surface tension (when compared to water) combined with a higher conductivity (when compared to water and DMF) while maintaining sufficient viscosity. Additionally, it has a volatility that is considerably lower than DMF and similar to that of water, which allows for both sufficient stretching of the jet and drying of the fiber prior to collection during the electrospinning process.

2.3.4 Electrospinning of Methyl-beta-cyclodextrin

We have established that, with sufficient molecular cohesion, chemically-modified cyclodextrins can be electrospun to produce fibers. In order to determine whether this is an anomaly related to the particular type of chemical modification, the potential to produce fibers from Methyl-beta-cyclodextrin (MβCD) was explored. MβCD is produced by substituting the hydroxyl- groups present on natural Beta-cyclodextrin with methyl- groups, producing ether functionalities in the glucose repeating units of the CD (Figure 2.11 inset). As with HPβCD, these methyl groups prevent intramolecular hydrogen bonding from occurring, leading to a higher solubility in water and an increase the hydration number, $m$, mentioned previously. Shikata and workers$^{54}$ determined that the hydration number increased from $5.9 \pm 0.3$ to $10 \pm 0.3$ for 55% substituted MβCD over natural cyclodextrins.
The particular MβCD studied here is identical to Shikata’s where an average degree of substitution of \( \sim11.5 \) or \( \sim55\% \) of the –OH groups were substituted by –CH\(_3\) groups.

In order to determine the impact of hydrogen bonding, indicated by the large hydration numbers, various quantities of urea was added and the resultant viscosities were measured (Figure 2.11). As aforementioned, urea is a well known hydrogen bond disruptor as demonstrated earlier with HPβCD\(^{53}\). Again, urea proved effective in disrupting hydrogen bonds in solution reducing the viscosity suggesting that a strong hydrogen bonding network is forming. It may be possible to exploit the hydrogen bonding capability of MβCD potentially providing enough molecular cohesion to electrospin fibers akin to aqueous HPβCD solutions.

The corresponding SEM micrographs of electrospun of aqueous MβCD solutions at various concentrations are shown in Figure 2.12. Fibrous material was produced starting at 60% MβCD (Figure 2.12a), however, it appears to be non-continuous, having many defects and bead-like formations. As the concentration of MβCD is increased to 65% (Figure 2.12b), the fibers become more regular and uniform with fewer defects and by further increasing the concentration to 70% MβCD (Figure 2.12c) gives continuous uniform defect free fibers as comparable to the results for HPβCD (Figure 2.3). However, there appears to be a larger window for producing fibers with MβCD (60-70%) then with HPβCD (65-70%). It is often a combined effect of surface tension, conductivity and viscosity that determines the window for which solutions can be electrospun\(^{13, 56}\). The parameters and fibers sizes for the
electrospun aqueous MβCD solutions are presented in Table 2.3. The viscosities for the two CD species (Table 2.1 and Table 2.3), at the same respective concentrations, are comparable. This finding is not surprising since the hydration values for the two species were found to also be identical (10 ± 0.3 mol water/mol repeat glucose)$^{54}$, so it is not unexpected for the behavior in solution to be very similar.

The large variance in fiber size and morphology between the two species should then be dictated by electrical conductivity and surface tension. The measured electrical conductivities were vastly different for the two CD species in solution. Methyl chloride is one of the components used in the synthesis of MβCD, which leads to a small amount (2%) of chloride ions as an impurity. These residual chloride ions serve to increase the conductivity greatly for MβCD in solution to more than 2-orders of magnitude higher to that of equivalent HPβCD aqueous solutions. An increase in conductivity allows for a higher surface charge density to be maintained on the jet and as a result promotes improved stretching during the electrospinning process$^{58}$. Additionally, the surface tension for MβCD solutions was found to be approximately 15% lower, on average, than complementary HPβCD solutions$^{59}$. Therefore we surmise that a higher electrical combined with a lower surface tension to be responsible for both the larger electrospinnability window and the reduced fiber diameters of MβCD when compared to HPβCD.
2.3.5 Electrospun Fiber Structure

A closer look at the structure of an electrospun nanofiber of HPβCD using high resolution TEM (Figure 2.13) again confirm that submicron fibers of HPβCD were electrospun from 65 wt% aqueous solutions. The fiber surface appears rough but shows a patterned morphology at the higher magnification (Figure 2.13b) possibly indicating presence of a self-assembled structure. The dimensions of the individual features seen in Figure 2.13b are similar to the dimensions of individual CD molecules. No electron diffraction pattern was obtained from the samples indicating that the fibers are amorphous as expected.

2.4 Conclusions

In summary, this study provides the first report of electrospinning a small molecule oligosaccharide HPβCD into submicron fibers. Defect-free fibers are obtained at high HPβCD concentrations (65-70 wt%), thereby creating an advantageous high throughput process. The ability to electrospin these solutions is attributed to hydrogen bonding aggregation between HPβCD molecules at high concentrations, as evidenced from presence of only bound water, an exponential increase in zero-shear viscosity at these concentrations and disruption of fiber formation upon addition of a hydrogen bond breaking agent (urea) to the system.
Additionally, we demonstrated that HPβCD could be electrospun in an array of solvents (water, formic acid and dimethylformamide) indicating potential uses in mixed solute/solvent systems for creating novel, versatile materials through electrospinning. The use of formic acid as a solvent proved advantageous over the other solvents owing to its low surface tension, high dielectric constant and its intermediate volatility.

We also established that other chemically modified cyclodextrins could be electrospun. Methyl-beta-cyclodextrin was electrospun to produce fibers at concentrations between 60-70 wt% in water. There was both a larger window for producing fibers and a reduction if fiber diameter at equivalent concentrations for MβCD when compared to HPβCD. This was due to the lower surface tension and higher electrical conductivity of the electrospinning solutions of MβCD. These findings suggest that electrospinning of HPβCD may be enhanced with the addition of ionic species (i.e. salts) in order to raise the electrical conductivity and potentially aid in controlling the final fiber diameter.

Our results of obtaining fibers from small molecules are significant as they point to new considerations as to what might be electrospinnable materials. Moreover, creating fibers made of CDs can generate new and “smart” applications for these unique molecules in a wide variety of fields.
2.5 References


Figure 2. 1: a) Chemical structure of hydroxypropyl beta-cyclodextrin. b) Approximate dimensions of the toroid formed by beta-cyclodextrin reproduced from (18).
Figure 2.2: SEM micrographs of electrospun HPβCD solutions of a) 50 wt%, b) 60 wt%, c) 65 wt%, and d) 70 wt%.
Figure 2.3: Effect of HPβCD concentration on the conductivity of aqueous solutions.

Figure 2.4: SEM micrographs of electrospun HPβCD fibers spun from solutions of a) 70 wt% HPβCD and 70 wt% HPβCD adding b) 10 wt% and c) 20 wt% urea.
Figure 2.5: Viscosity ($\eta$) versus shear stress ($\tau$) of precursor solutions for electrospinning of both neat HP\textbeta CD and HP\textbeta CD with various amounts of urea (structure inset).
Figure 2.6: Zero-shear viscosity for HPβCD solutions of interest, the increase in viscosity is a result of the self-assembly of the HPβCD molecules via hydrogen bonding. The cartoons (not drawn to scale) show how the aggregates may grow larger with increasing HPβCD to the point where they have enough cohesion/entanglement above 65 wt% to stretch into fibers.
Figure 2.7: Determination of the bound water in HPβCD solutions by DSC: a) DSC thermograms of the HPβCD solutions with different concentrations and b) amount of bound water present as a function of HPβCD solution concentration.

Figure 2.8: Structure for natural beta-cyclodextrin with the location of the secondary and primary along with the carbons discussed labeled.
Figure 2.9: Hydration number as a function of HPβCD in water calculated from DSC bound water experiments.
Figure 2.10: SEM micrographs of electrospun HPβCD from: a) 50\% and b) 60\% in DMF and c) 50\% and d) 60\% in Formic Acid.
Figure 2.11: Viscosity ($\eta$) versus shear stress ($\tau$) of precursor solutions for electrospinning of both neat MβCD (structure inset) and MβCD with various amounts of urea.

Figure 2.12: SEM micrographs of electrospun MβCD from aqueous solutions containing a) 60%, b) 65%, and c) 70% MβCD.
Figure 2.13: TEM micrographs showing fibers electrospun from a 65 wt% solution at two magnifications a) 200 kX and b) 400 kX.

Table 2.1 A summary of the solution viscosities, fiber morphology and size produced at different aqueous HPβCD concentrations. The average fiber diameters along with their standard deviations are listed.

<table>
<thead>
<tr>
<th>Concentration (HPβCD)</th>
<th>Viscosity (Pa-s)</th>
<th>Morphology</th>
<th>Fiber Diameter (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 wt%</td>
<td>0.041 ± 0.008</td>
<td>Large beads only</td>
<td>NA</td>
</tr>
<tr>
<td>60 wt%</td>
<td>0.247 ± 0.011</td>
<td>Beads connected with fibers</td>
<td>269.6 ± 154.4</td>
</tr>
<tr>
<td>65 wt%</td>
<td>1.131 ± 0.021</td>
<td>Small defects, large size variability</td>
<td>933.3 ± 778.7</td>
</tr>
<tr>
<td>70 wt%</td>
<td>3.514 ± 0.043</td>
<td>Defect free fibers</td>
<td>989.7 ± 117.2</td>
</tr>
</tbody>
</table>
Table 2.2: Summary of the solution parameters for HPβCD solutions of indicated concentrations in their respective solvents which produce fibers with the diameters listed.

<table>
<thead>
<tr>
<th>Concentration (wt%)</th>
<th>Solvent</th>
<th>Viscosity (Pa-s)</th>
<th>Conductivity (μS/cm)</th>
<th>Fiber Diameter (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>DMF</td>
<td>0.231 ± 0.012</td>
<td>0.93 ± 0.03</td>
<td>--</td>
</tr>
<tr>
<td>60</td>
<td>DMF</td>
<td>2.782 ± 0.022</td>
<td>0.33 ± 0.02</td>
<td>1979 ± 642</td>
</tr>
<tr>
<td>50</td>
<td>FA</td>
<td>0.171 ± 0.016</td>
<td>90.31 ± 0.1</td>
<td>301 ± 122</td>
</tr>
<tr>
<td>60</td>
<td>FA</td>
<td>2.053 ± 0.023</td>
<td>42.23 ± 0.2</td>
<td>572 ± 165</td>
</tr>
</tbody>
</table>

Table 2.3: Summary of solution parameters and fiber diameters for electrospun MβCD at indicated concentrations in water.

<table>
<thead>
<tr>
<th>Concentration (wt%)</th>
<th>Viscosity (Pa-s)</th>
<th>Conductivity (μS/cm)</th>
<th>Fiber Diameter (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>0.172 ± 0.021</td>
<td>1492.2 ± 0.5</td>
<td>228 ± 102</td>
</tr>
<tr>
<td>65</td>
<td>0.873 ± 0.065</td>
<td>1079.3 ± 0.7</td>
<td>143 ± 47</td>
</tr>
<tr>
<td>70</td>
<td>2.924 ± 0.058</td>
<td>617.5 ± 0.4</td>
<td>444 ± 59</td>
</tr>
</tbody>
</table>
CHAPTER 3

Multi-Functional Nanofibers from Electrospinning of Cyclodextrin/Poly (vinyl alcohol) Blends
Multi-Functional Nanofibers from Electrospinning of Cyclodextrin/Poly (vinyl alcohol) Blends

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3.1 Introduction

Electrospinning is a practical and simple method for producing nanofibers that has gained much attention over the past few decades. This technique has been used to produce functional nanofibers from various materials including polymers, polymer blends, composites and ceramics\textsuperscript{1-8}. The resulting nonwoven fiber mats possess a high surface to volume ratio and a high degree of porosity along with small pore sizes. These features render them extremely useful in a host of applications including filtration devices\textsuperscript{9-11}, tissue scaffolds\textsuperscript{12-14}, protective clothing\textsuperscript{11,15} and reinforced composites\textsuperscript{16,17}.

Incorporating cyclodextrins into nanofibers creates an interesting opportunity for producing functional materials. Cyclodextrins (CDs) are ring-shaped sugar molecules possessing a hydrophobic cavity and a hydrophilic exterior which imparts them with water solubility (Figure 3.1). There are three main types of naturally occurring cyclodextrins namely $\alpha$-, $\beta$-, and $\gamma$- which have 6, 7 and 8 member rings, respectively. Owing to their hydrophobic interior, cyclodextrin molecules can form noncovalent host-guest interactions which allow for complexation with poorly water soluble small molecules and

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macromolecules. The complexation efficiency and stability between the host and guest depend on factors such as shape/size and specific functionalities that create binding forces with the CDs via hydrophobic interactions, and van der Waals and electrostatic forces. The ability to complex with these various types of molecules make CDs useful for a variety of applications such as in drug delivery (stabilization and solubility of drugs, bioavailability, controlled release, masking of undesirable taste, and drug toxicity reduction), foods (flavor stability and release and masking of undesirable tastes), textiles (stability and release of various additives), and filtration (cholesterol, heavy metals and organic compounds).

Integrating CDs could expand the utility of nanofibers by leveraging the high aspect ratio of nano-scale fibers with the functionality of CDs. Although several groups have studied blending of CDs and various polymers, the area is still relatively unexplored. Uyar et al. studied the incorporation of the three most common natural CDs α, β, and γ (25 and 50 w/w) into polyethylene oxide (PEO) to create functional nanofibers. They found that the addition of CDs to the PEO solutions facilitated bead-free electrospinning resulting from an increase in viscosity and conductivity. Moreover, they explored the incorporation of CDs into poly (methyl methacrylate) (PMMA) and polystyrene (PS) nanofibers in order to create functional nanowebs. β-CDs have been used to crosslink poly (acrylic acid) nanofibers in order to render the fibers water insoluble. Additionally, poly (N-vinylpyrrolidone) (PVP) nanofibers containing gold nanoparticles have been produced utilizing β-CD as both a stabilizing and reducing agent. PMMA nanofibers containing...
phenylcarbomylated β-CD have been electrospun for use in waste treatment. Furthermore, polyvinyl chloride (PVC) nanofibers were electrospun containing a catalyst for the detoxification of nerve agents synthesized from β-CD and o-iodosobenzoic acid with the goal of creating protection from chemical warfare\textsuperscript{15}.

In our previous work (Chapter 2), we demonstrated that chemically modified cyclodextrins, hydroxypropyl (HPβCD), (structure shown in Figure 3.1) and methylated (MβCD) β-cyclodextrins, can be electrospun into fibers without the use of polymers as a carrier. However, since very high concentrations are necessary to electrospin (60-70 wt% in solution) there is a very small window in which to make fibers before the solution becomes too viscous to electrospin. This constraint permits only a very narrow range of fiber diameters.

In this study, we illustrate that this can be overcome by adding a small amount of compatible polymer, poly (vinyl alcohol) (PVA), while modulating cyclodextrin concentrations allows for tailoring of both cyclodextrin loading and fiber diameters. Additionally, we are the first to report electrospun cyclodextrin/polymer blended fibers with an excess of 50% (w/w fiber) cyclodextrin loading. Furthermore, we can take advantage of the hydroxyl- group functionalities present on both PVA and HPβCD that provide a unique opportunity to crosslink these blended fibers to form high surface area hydrogels that could be used as interesting molecular filters or for capture and release. Ethylene glycol diglycidyl ether (EGDE) has been shown to be a suitable crosslinker for HPβCD in solution and ex-
situ for fibers made of elastin\textsuperscript{45}. Herein we show its capacity to crosslink as-spun fiber blends of PVA/HP\(\beta\)CD to produce hydrogels that maintain fibrous morphologies even after soaking in water for 24 hours.

3.2 Experimental

Polyvinyl alcohol was purchased from Sigma-Aldrich (Mowiol 40-88\textsuperscript{®}) Hydroxypropyl-\(\beta\)-cyclodextrin was purchased from CTD, Inc (High Springs, Fl, technical grade, product code THPB-T) and were used without further purification. The average hydrolysis for this PVA is 88\%, meaning 12\% of the acetyl groups remain due to its production from vinyl acetate. The purity of THPB-T grade HP\(\beta\)CD is 91.2\%, and includes the presence of impurities such as water (3.4\%), propylene glycol (<5.0\%) and unsubstituted \(\beta\)-CD (<1.0\%). The average degree of substitution for this derivative was 5.6 (computed mol. wt.-1460). All solutions were made with deionized water.

The HP\(\beta\)CD and PVA solutions were made fresh by adding the respective amounts of CD with supplemental water and allowed to mix in a shaker bath overnight at 35\(^\circ\)C and 60 \(^\circ\)C, respectively, in order to expedite dissolution. All solutions were stored in a refrigerator when not being used to prevent any degradation. Different blend ratios were made by adding various amounts of these stock solutions together as needed and then were mixed at 35 \(^\circ\)C yielding homogenous solutions displaying no turbidity. Physical mixtures were cyro-ball milled in liquid nitrogen for 5 minutes each. They were then mixed in the specified amounts and ball-milled together to mix well or tested separately as is.
All rheological experiments were performed at 25 °C in a TA Instruments AR-2000 stress controlled rheometer using cone and plate geometry. All rheological measurements were performed in triplicate to ensure reproducibility within ±5%. Calorimetry studies were done on the HPβCD solutions using a TA instruments® Q2000 Differential Scanning Calorimeter. Each sample (8-12 mg) was loaded into an aluminum pan and crimped. The samples were ramped from room temperature to 250 °C, held isothermally for 5 min, then ramped back to room temperature, and finally ramped back to 250 °C for a second heating, the ramp rate used was 10 °C/min. The glass transition temperature was determined from the inflection point of the specific heat capacity of the second scan.

Surface tension measurements at the air/surfactant solution interface were made by the Wilhelmy plate method using a platinum rectangular thin blade. The blade was hooked to a sensitive force transducer. The measured surface tensions of pure water and acetone matched literature values. The electrical conductivity was measured using an EC meter (Fisher Accumet BASIC AB30).

The electrospinning setup consisted of an aluminum collector plate, a precision syringe pump (Harvard Apparatus, Holliston, MA), and a high-voltage power supply (Gamma High Voltage Research, model D-ES30 PN/M692 with a positive polarity). The syringe pump controlled the flow of polymer solution to a metallic needle (22G) which was connected to the positive electrode of the power supply. The collector plate was grounded, and the fibers were collected on an aluminum foil wrapped on the collector plate. The tip-to-
collector distance and solution flow rate were fixed at 12 cm and 0.5 mL/h, respectively, and the applied voltage ranged between 5 and 11 kV. The electrospun fibers obtained were gold-sputtered, and SEM measurements were obtained on a Hitachi S-3200 or FEI XL30 scanning electron microscope. The average fiber diameter was determined by measuring fiber diameters of at least 100 individual fibers from multiple SEM images using ImageJ software provided by NIH.

Fourier transform infrared spectroscopy (FTIR) studies were performed by a Nicolet 6700 FTIR spectroscope (Thermo Electron Corp) (Infrared spectra (400-4000 cm\(^{-1}\)) and the XRD studies were carried out using a Philips X'Pert PRO MRD HR XRD System.

Crosslinking experiments were carried out by cutting a small piece (~2-3 mg) of fiber mat and immersing it in EGDE (99%, Sigma Aldrich) and setting the pH to ~11 (by adding NaOH) overnight at 50 °C. The mats were then washed and placed in a large beaker to soak overnight followed by drying.

### 3.3 Results and Discussion

#### 3.3.1 Electrospinning of PVA/HPβCD solutions

Figure 3.2 shows the SEM micrographs of fibers made from various concentrations (w/w) of PVA, HPβCD and PVA/HPβCD blends. We find that electrospinning PVA alone in concentrations up to 2% (w/w) (Fig 3.2 a,f, k, and p) produces only defective fibrous material due to the low solution viscosities (6.3 ± 0.02 cP). Electrospinning of HPβCD at solution
concentrations of up to 60% (w/w) (Fig. 3.2 a-e) produces only beaded structures consistent with our previous work where fibers were not achieved until a concentration of 65% (w/w). However, by blending the two materials, an array of morphologies can be produced. By adding relatively small amounts of PVA to increasing amounts of HPβCD bead-free fibers can be achieved (Fig 3.2 r, i, and j). Table 3.1 summarizes the solution properties and the morphological results of generally defect-free electrospun PVA and PVA/HPβCD nanofibers with their respective fiber diameters.

In the electrospinning process, the solution viscosity, conductivity and surface tension have been found to be important in dictating the as-spun fiber morphology and diameter. In general, a viscous, conductive solution with a low surface tension facilitates the production of defect free nanofibers. We find that, in all cases studied here, the addition of PVA to the HPβCD solutions results in an increase of viscosity and conductivity.

3.3.1.1 Effect of Surface Tension

Surface tension is the primary force that opposes coulombic repulsion and plays a role in the electrospinnability of a solution. It is often a combined effect of surface tension and viscosity that determines the window for which solutions can be electrospun. Often the surface tension of a particular solution can be controlled by careful selection of the solvent; however, on changing the solvent composition the viscosity and conductivity are often altered as well. Therefore it is difficult to isolate the effect of surface tension alone. In our case the surface tension of the solutions is not drastically different from sample to
The lowest surface tension was observed for solutions containing only PVA (52.7 ± 0.7 dynes/cm) while the highest was seen for 70% HPβCD solution (58 ± 0.8 dynes/cm). The small change in surface tension amongst the samples studied allows for a more discriminating examination of other effects, namely viscosity and electrical conductivity.

3.3.1.2 Effect of Viscosity

The addition of PVA introduces species in the solutions that not only is capable of hydrogen bonding but also forming entanglements. This can be best illustrated by comparing the effects of the addition of PVA on the specific viscosity (ηsp) of aqueous solutions that contain constant amounts of HPβCD to the specific viscosity of aqueous solutions containing only HPβCD (Figure 3.3). Specific viscosity expresses the incremental viscosity due to the addition of polymer to the solution and is defined as:

\[ \eta_{sp} = \frac{\eta - \eta_o}{\eta_o} \]  \hspace{1cm} (3.1)

Here \( \eta \) is the viscosity of the solution and \( \eta_o \) is the viscosity of the solvent\(^47\). Entanglement concentration (C_e) is defined as the transition for the semi-dilute unentangled regime to the semi-dilute entangled regime indicated by a shift in slope of \( \eta_{sp} \)\(^48\). For a neutral, linear, non-associating polymer the slope dependence is \( \eta_{sp} \sim C^{1.25} \) for the semi-dilute unentangled regime and \( \eta_{sp} \sim C^{3.8} \) for the semi-dilute entangle regime in a good solvent\(^49\). A summary of the parameters found by fitting the slopes of data for \( \eta_{sp} \) vs. concentration of PVA (w/w) from Fig. 3.3a is presented in Table 3.2.
As previously mentioned, the theoretical slopes for the semi-dilute unentangled regime and semi-dilute entangled regime are ~1.25 and ~3.8 which is in agreement with our findings for PVA solutions. However, the slopes change systematically with the addition of increasing amounts of HPβCD in solution. In general, solvent quality doesn’t affect the \( C_e \), however it does have an effect on the slopes in the respective regimes\(^5\). Typically, \( \eta_p \) increases in the dilute or semi-dilute unentangled regime with increasing solvent quality due to stronger apparent repulsive forces between chain segments but decreases with solvent quality in the semi-dilute entangled regime due to a lower number of entanglement couplings in a good solvent\(^5\). In the PVA/HPβCD solutions we see a reduction in slopes for both regimes and a shift in \( C_e \) to a lower PVA concentration. A reduction in the semi-dilute unentangled regime could be a manifestation of a general effect of an increased base viscosity due to the concentration of HPβCD in the solutions with the polymer having a lesser effect in this regime owing to the lack of entanglements. The reduction in slope above \( C_e \) may be analogous to increasing the solvent quality as the polymer is now interacting with the co-solute (HPβCD) having a similar effect to increasing the solvent quality and reducing the number of polymer entanglements. The shift in \( C_e \) is a result of strong interactions between the PVA and HPβCD. Figure 3.3b illustrates that the increase of \( \eta_p \) with HPβCD concentration is relatively weak until a concentration higher than 50% (w/w) due to a robustly hydrogen bonded system\(^5\). With the addition of a polymer capable of hydrogen bonding the transition in slope is shifted to a lower concentration as PVA and HPβCD show a synergistic effect on \( C_e \).
McKee et al. found that for copolyesters, the minimum concentration for producing beaded fibers was the $C_e$ and the minimum concentration for achieve defect free fibers was 2-2.5 times $C_e$. In Table 3.2, the minimum concentration of PVA (w/w) necessary for the onset for uniform fiber production is listed for each solution combination. For our system (PVA (2.5$C_e$), 20%HPβCD/PVA (2.35$C_e$), 30%HPβCD/PVA (2.72$C_e$), and 40%HPβCD/PVA (2.5$C_e$)) the factor of 2-2.5 times the $C_e$ correlates well, indicating that, for a non-traditional electrospinning system, that contains a polymer and small molecule, the onset of uniform fiber production can be predicted based on shear rheological properties of the electrospinning solutions. Additionally, it can be seen in Table 3.1 that although some of the electrospinning solutions have similar viscosities (i.e., solutions (20/4 (176 ± 15 cP) and 0/6 (185 ± 3 cP)) and (60/0.1 (359 ± 25) and 6/6 (344 ± 5 cP))) however, the resultant defect-free fiber diameters (i.e., solutions (20/4 (590 ± 85 nm) and 0/6 (233 ± 33 nm)) and (60/0.1 (1325 ± 515.2 nm) and 6/6 (409 ± 44)) differ significantly. These results indicate that the shear viscosity isn’t the only parameter important in dictating the final fiber morphology.

### 3.3.1.3 Effect of Conductivity

Conductivity is another important parameter in the electrospinning process as it fundamentally requires the transfer of electric charge from the electrode to the droplet at the apex of the tip. A minimal electrical conductivity is necessary for a solution to be electrospinnable as a solution with zero conductivity could not be electrospun. The effect of
the concentrations of HPβCD and PVA on aqueous solution conductivities can be seen in Figure 3.3. The conductivity of the HPβCD solutions is relatively unchanged at lower concentrations (10-30% (w/w)), after which it declines linearly with concentration. This is due in part to a reduction in the mobility of the bulk water. In both our work and others, the amount of bound water increases with the HPβCD concentration, shown by a reduction in available freezable water. Shikata et al. found that water molecules are tightly bound to hydrated CDs in aqueous solutions and possess exchange relaxation and residence times longer than the rotational relaxation strengths for water molecules in the bulk state. This effect is amplified by the addition of substituted hydroxypropyl groups on the CDs due to a reduction in intramolecular side-by-side hydrogen bond linkages found in natural cyclodextrin due to steric effects. Foster et al. reported a reduction in transport properties (including conductivity) in polymer solutions containing PEO which deviated from ideal due to the hydration of PEO and a decrease in bulk water. It should be noted that a related effect of the bound water molecules, hydrating the HPβCD, demonstrate a decrease in conductivity, while resulting in an increase viscosity of the aqueous as the plots inversely mirror each other.

The addition of PVA to the water increases the conductivity due to an increase in ionic groups (also due to impurities or additives in the as-received bulk PVA). The slope of the conductivity seen in Figure 3.4b begins to plateau at higher concentrations of PVA (10% w/w) owing to an increase in viscosity and its ability to bind water. In our system, an increase of PVA in the blends always resulted in a higher conductivity, however it is worth
noting that the magnitude of the conductivity was not additive but rather dominated by the presence of large amounts of HPβCD (>20% (w/w)) due to hydrogen bonding between PVA and HPβCD, mitigating the consequence of adding ionic groups. The result of higher conductivity on the fiber morphology is reflected by a reduction in fiber diameter for aforementioned solutions (0/6 (195 ± 1.2 μs/cm) vs. 20/4 (95.2 ± 0.7 μs/cm)) and (6/6 (183 ± 0.9 μs/cm) vs. 40/2 (31.5 ± 0.4 μs/cm)) possessing comparable viscosities but notably different conductivities. An increase in the conductivity of the solution aids in reducing the fiber diameter given that the solutions would carry a greater charge and be subjected to higher stretching under the high electric field1,56,57.

3.3.1.4 Other Solution Effects

The flexibility of the system to create fibers that are the same composition but different fiber diameters is shown in Table 3.1 (solutions 6/6 (409 ± 41 nm) and 8/8 (750 ± 55). Based on these results it is feasible that this system could be tailored by modulating both the overall concentrations of the system and the ratio of the two components to produce a range of fiber diameters within the range of compositions the limitation being that the blends are 2-2.5 times the Cc as shown previously.

In addition to viscosity, the viscoelasticity of the electrospinning solutions may be of interest. Yu et al. studied the role of solution elasticity in the formation of electrospun fibers by blending small amounts of high molecular weight PEO with concentrated aqueous solutions of low molecular weight polyethylene glycol (PEG)58. The extensional viscosity
and longest relaxation time were measured using a capillary breakup extensional rheometer (CaBER). They observed that by adding small amounts of the elastic PEO (0.1-0.2% (w/w)) to PEG solutions and increasing the Deborah number (De), the ratio of the fluid relaxation time to the instability growth time, and suppressing the Rayleigh instability, but maintaining the same polymer concentration, surface tension, zero shear viscosity, and conductivity, they could transition from producing beaded fibers to uniform fibers. In Figure 3.5, the fiber morphology of the mats spun from 60 wt% HPβCD and 60 wt% HPβCD/0.1 wt% PVA. As shown from our previous work, aqueous solutions containing 60 wt% HPβCD produce only large beaded structures with some fibrous material, similar to what Yu et al. saw when electrospinning high concentrations of PEG. However, a transition to uniform fibers is seen with the addition of a viscoelastic polymer, 0.1 wt% PVA59. Like Yu’s findings, the polymer concentration, surface tension, electrical conductivity and viscosity (< 50 cP) remain virtually unchanged. This indicates that in addition to the aforesaid parameters, solution viscoelasticity also may play an important role in the formation of fibers for our system.

Finally, we have considered the possibility of complexation between the PVA and HPβCD, that is, the potential threading of PVA chains into the HPβCD core to form inclusion complexes (IC). Harada et al. conjectured that, due to the hydrophilicity of PVA, it is not favorable for PVA to thread natural cyclodextrins (α, β, and γ-cyclodextrins) evidenced by the absence of solution turbidity and lack of crystalline ICs after blending60. However, Hernández et al. established that ICs did form between PVA and γ-CDs owing to a change in the thermal and crystalline (i.e. x-ray diffraction patterns (XRD)) properties of
films produced via solution casting. Additionally, the authors found that α-CDs did not form ICs with PVA, attributed to the smaller size of the α-CD cavity (~0.47-0.53 Å). It should be noted that β-CD complexation with PVA was not studied here. Furthermore, based on calculations of the bond lengths, (C-C) 1.54 Å, (C-O) 1.43 Å, (C-H) 1.10 Å, and (O-H) 0.95 Å, and bond angles (C-C-C), (C-C-O), (C-C-H), and (C-O-H) 109.5, and the fact that PVA chain backbones have a planar zigzag conformation with a repeat of 2.52 Å indeed PVA could fit inside of the HPβCD cavity (~6-6.5 Å). Horsky studied the viscometric detection of ICs between PVA and HPβCD and found that, although the viscosity of the blended solutions did exhibit a significant increase, the results were inconclusive being that it is difficult to separate the general effects of adding PVA to the HPβCD solutions from a complexation effect. Although we see a considerable effect on the viscosity upon addition of PVA to HPβCD solutions, it is not necessarily an indication of complexation and could be the effect of the formation of a strong hydrogen bonded network. In order to further surmise the potential complexation of HPβCD with PVA, we must study the properties of as spun blended fibers.

3.3.2 Properties of PVA/HPβCD fibers

3.3.2.1 FTIR analysis

The presence of HPβCD in the electrospun mats was confirmed by FTIR studies. The FTIR spectra of HPβCD, PVA and blended fibers are shown in Figure 3.6. The overlap
of adsorption peaks due to some similarities of the two species makes it difficult to elucidate
the individual components of each component in the blends. However, visible adsorption
bands from HPβCD at ~1030, ~1080, and ~1155 cm$^{-1}$ (due to coupled C-C/C-O stretching
and antisymmetric stretching vibrations of the C-O-C glycosidic bridge)\textsuperscript{65} can be seen for all
of the blends of PVA/CD mats indicating successful incorporation of HPβCD into the fibers

3.3.2.2 TGA analysis

The TGA scans for HPβCD, PVA, and HPβCD /PVA (50/50) blends are presented in
Figure 3.7. The blends, as indicated, are in the form of as-spun fiber and physical mixture
(cryo-ball milled prepared as described in the Experimental Section). We can see that the
main decomposition of the HPβCD /PVA blends (50/50) is ~295 °C and 300 °C for the as-
spun fibers and physical mixture, respectively, which is an intermediate of PVA (277 °C) and
HPβCD (322 °C). The phenomenon of a higher decomposition temperature for polymer-CD
ICs could imply that the PVA chains are included inside polymer-CD IC channels resulting
improving the thermal stability PVA\textsuperscript{61}. However, in this case, the physical mixture of the
two components shows a comparable decomposition temperature to that of the electrospun
fibers. Furthermore, it is has been shown that although physical mixtures of CDs and
polymers can complex, the degree of complexation is expected to be much lower than that of
a solution cast film or electrospun fiber. These findings indicate that decomposition
temperature of the electrospun blend is due to more of a general effect of mixing the two
components. It’s speculated that the minor differences between the decompositions are due
to the morphology and higher degree of intimate mixing of the components of the electrospun fibers when compared to the physical mixture and not due ICs being formed between the polymer and CD\textsuperscript{66}.

### 3.3.2.3 DSC and XRD analysis

DSC analysis is one convenient method to determine the miscibility and crystallinity present in polymer blends. The DSC thermograms of the HP\(\beta\)CD, PVA, and HP\(\beta\)CD/PVA blends are shown in Figure 3.8. Calorimetry experiments were run at temperatures up to 250\(\degree\)C in order to prevent degradation of PVA and HP\(\beta\)CD. Included here are the first and second heating scans in order to determine the crystallinity of the as-spun fibers. The degree of crystallinity was calculated by dividing \(\Delta H\) by the heat required for melting a 100% crystalline PVA sample (\(\Delta H_{c} = 138.6\ J/g\)) and is summarized in Table 3.3. In general fibers display a higher crystallinity than films that may be due to a partial drawing effect on the polymer chains during electrospinning facilitating the formation of crystallites\textsuperscript{66}.

Since HP\(\beta\)CD is an amorphous solid, we only examine the crystallinity of the PVA present in the fibers. The PVA crystallinity shows a general decrease with the addition of HP\(\beta\)CD to the system. Hydrogen bonding can have a significant effect on the thermal properties of polymer blends. Melting point (\(T_{m}\)) depression is seen in polymer blends where the amorphous phase is a miscible blend. In blends where one component crystallizes, the \(T_{m}\) depression is larger for systems with interactions than without specific interactions\textsuperscript{67, 68}. In each blend, a single glass transition temperature (\(T_{g}\)) is seen (Fig 3.8b), strongly
suggesting that the blends are fully miscible with a homogenous amorphous phase resulting in a lower melting point and crystallinity than in the neat PVA fibers. During the first heating (Fig 3.8a) the large broad endothermic peak between 50-100 °C (near the T_g of PVA ~72 °C) is due to the elimination of a volatile component (water) remaining in the fibers and makes the determination of the T_g difficult. Therefore, a second heating (Fig 3.8b) is employed to elucidate the T_g for each of the samples. To gain some measure of the extent of interactions occurring in the system due to hydrogen bonding it was of interest to test the deviation of the T_g's from ideal behavior. Consequently, the T_g value is predicted using the Gordon-Taylor equation which assumes the blend is miscible and that the free volumes are additive^69:

$$T_{g12} = \frac{w_1 T_{g1} + Kw_2 T_{g2}}{w_1 + Kw_2}$$ (2)

where w_1 and w_2 are the weight fractions and T_{g1} and T_{g2} are the respective glass transition temperatures for HPβCD and PVA experimentally determined to be 225 °C and 72 °C. The constant K is related to the free volume of the system and is calculated using the Simha-Boyer rule^70:

$$K = \frac{T_{g1} \rho_1}{T_{g2} \rho_2}$$ (3)

where ρ_1 and ρ_2 are the densities of the pure components taken from the literature. The density of HPβCD is estimated by using that of glucose (1.53 kg/m^3) and the density of PVA
was found from the literature (1.23 kg/m$^3$). The T$_g$s determined experimentally are displayed in Figure 3.9 with the solid line representing the T$_g$ using eq.4. Positive and negative deviations from ideal T$_g$s calculated using Eq.4 prove that specific interactions are occurring within the polymer blends, via hydrogen bonding.

Another method commonly used to study the phases of polymer blends is XRD. The x-ray diffraction spectra of PVA, HP$\beta$CD and the 50/50 blend of the two are shown in Figure 3.10. The key features of semi-crystalline PVA are seen due the presence of a peak at 2$\theta$ = 20° and the amorphous nature of HP$\beta$CD characterized by broad amorphous halos present at 2$\theta$ = 8° and 2$\theta$ = 18° with no sharp crystalline peaks visible. The 50/50 blend displays an additive nature of both species and a peak at 2$\theta$ = 8°, indicating a channel-type structure usually associated with polymer ICs is not present$^{61}$.

Again, the possibility of complexation between PVA and HP$\beta$CD is considered. Hernandez saw a decrease in the melting temperature and crystallinity when studying the ICs of complexed PVA and natural $\gamma$-CDs attributed to the inclusion of some of the PVA chains within the $\gamma$-CD preventing associations of some of the polymer chains and the ability to crystallize as efficiently. We too see a reduction in the melting temperature and crystallinity when compared to neat PVA fibers based on our experimental data presented in Table 3.3, however, it is difficult to decouple the effect of potential complexation from the general effects of blending mentioned above. XRD patterns do not shed any light on the issue as we
see the typical peaks from PVA and the amorphous nature of HPβCD without any additional salient peaks indicating complexation.

### 3.3.3 Crosslinking of PVA/HPβCD Fibers

The extraordinary solubility of HPβCD aids in its flexibility for electrospinning and tailoring of bicomponent ratios, however it limits the final fiber applications to fast dissolving membranes in aqueous environments. Therefore, a preliminary study on the ability to crosslink these fibers ex-situ (after spinning) to determine whether the fiber morphologies could be preserved after soaking in water overnight.

The cross-linking of PVA/HPβCD fibers was carried out in EGDE. Heating is required for the reaction to proceed; whereas at room temperature, no cross-linking is observed, therefore, based on the findings of Rodriguez et al, the crosslinking was carried out at 50 °C. At this temperature both the cyclodextrins and PVA remain stable; consequently these conditions were chosen to carry out the process. Figure 3.11 shows SEM micrographs of fibers that were crosslinked under these conditions and followed by soaking overnight in a water bath. In all cases, material remained after soaking. However, it appears that fibers with a higher content of PVA retain their morphology better. This could be due in part to the inherently lower solubility of neat PVA in water and the better mechanical properties (observed by handling the fibers and by visual inspection). It appears that at very high HPβCD content (90/10 and 100/0 HPβCD/PVA) the morphology of the fibers is mostly destroyed by soaking. It should be noted that due to the retention of EGDE residue after the
crosslinking process, it was very difficult to image them using electron microscopy due to the inability to dry the crosslinked product. Nevertheless, the preservation of any materials after soaking is promising in producing functional, water resistant submicron fibers containing CDs. This is the first step in many toward finding the best suitable conditions to crosslink these fibers as they need to be studied in more detail in the future.

3.4 Conclusions

Electrospinning of functional PVA/HPβCD blended fibers has been achieved. Uniform fibers with various blend ratios varying from neat 30% up to >99% HPβCD (w/w based on fiber content) were possible. We found that the blended solutions exhibit an “entanglement” at lower concentrations of PVA when increasing amounts of HPβCD are present allowing for the production of bead-free fibers. The effects of electrical conductivity and viscosity were exposed by holding other solution parameters constant. We observed that an increase in viscosity intuitively produced larger fiber diameters due to a resistance of stretching during the electrospinning process. Also, as expected, an increase in electrical conductivity improved fiber uniformity and decreased fiber diameter since the polymer jet would be subjected to higher stretching under the high electric field. Similarly, the effect of elasticity on fiber morphology was discussed.

FTIR confirmed the presence of HPβCD in the fibers while XRD and DSC results suggested that the two components form a miscible blend. WE believe that complexation, that is, threading of the PVA chains through the CD cavities does not occur due to a
similarity between the thermal decomposition of an intimate blend made via electrospinning and a physical mixture produced by cryo-ball milling and could not be confirmed by way of rheological or other means. The crystallinity of the PVA in the fibers showed a general decrease in the presence of HPβCD and could not be detected for blends with a higher than 50% (w/w) content of HPβCD.

HPβCD, PVA and bicomponent (HPβCD/PVA) fibers were crosslinked using EGDE at 50 °C. In all cases, materials were retained after soaking the crosslinked fibers in water overnight. The preservation of materials is a promising step toward the development of functional water resistant submicron fibers.
3.5 References


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Figure 3.1: The (a) chemical and (b) conformational structure of HPβCD.

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Figure 3.2: Evolution of electrospun PVA, HPβCD, and indicated blends (a-t) for various solution concentrations.
Figure 3.3: Specific viscosity of aqueous solutions containing (a) PVA and PVA/HPβCD blends and (b) HPβCD alone vs. concentration of the respective components.

Figure 3.4: Conductivity of aqueous solutions of (a) HPβCD and (b) PVA
Figure 3.5: Morphology of mats electrospun from a) 60 wt% HPβCD and b) 60 wt%/0.1 wt% PVA aqueous solutions.

Figure 3.6: FTIR spectra of HPβCD, PVA, and HPβCD/PVA blended fibers with the wavenumbers of interest indicated.
Figure 3.7: a) TGA scans and b) first derivative weight loss for HPβCD, PVA, and HPβCD blends (PM (physical mixture) and as spun fiber).

Figure 3.8: DSC thermograms for the a) first heating and b) second heating of HPβCD, PVA, and HPβCD/PVA blended fibers (exo up)
Figure 3.9: Comparison of experimentally found Tgs for HPβCD, PVA, and blends (solid squares) thereof with that of values calculated using eq.4.
Figure 3.10: X-ray diffraction patterns for PVA, HPβCD, and a 50/50 blend thereof.
Figure 3.11: SEM micrographs of a) 0/100, b) 30/70, c) 50/50, d) 70/30, e) 90/10, and f) 100/0 HPβCD/PVA fibers that have been crosslinked in EGDE at 50 °C for 8 hours than soaked in water overnight.
Table 3.1: Properties of PVA and PVA/HPβCD solutions and the resulting electrospun fibers.

<table>
<thead>
<tr>
<th>Solutions (HPβCD/PVA)</th>
<th>Viscosity (cP)</th>
<th>Conductivity (µs/cm)</th>
<th>Surface Tension (dynes/cm)</th>
<th>Morphology</th>
<th>Fiber Diameter (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/6 (0/100)</td>
<td>185 ± 7</td>
<td>195.2 ± 1.2</td>
<td>52.7 ± 0.7</td>
<td>nanofibers</td>
<td>233 ± 33</td>
</tr>
<tr>
<td>2.57/6 (30/70)</td>
<td>195 ± 9</td>
<td>180.5 ± 1.5</td>
<td>53.5 ± 0.5</td>
<td>nanofibers</td>
<td>345 ± 45</td>
</tr>
<tr>
<td>6/6 (50/50)</td>
<td>344 ± 10</td>
<td>183.1 ± 0.9</td>
<td>54.2 ± 0.8</td>
<td>nanofibers</td>
<td>409 ± 41</td>
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<tr>
<td>8/8 (50/50)</td>
<td>1141 ± 13</td>
<td>215.6 ± 1.7</td>
<td>54.3 ± 0.6</td>
<td>nanofibers</td>
<td>750 ± 55</td>
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<tr>
<td>14/6 (70/30)</td>
<td>554 ± 16</td>
<td>175.2 ± 1</td>
<td>54.5 ± 0.9</td>
<td>nanofibers</td>
<td>634 ± 35</td>
</tr>
<tr>
<td>20/4 (80/20)</td>
<td>176 ± 15</td>
<td>95.2 ± 0.7</td>
<td>57.8 ± 0.6</td>
<td>nanofibers</td>
<td>590 ± 85</td>
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<tr>
<td>30/3 (90/10)</td>
<td>213 ± 12</td>
<td>56.2 ± 0.9</td>
<td>58.6 ± 0.5</td>
<td>nanofibers</td>
<td>715 ± 102</td>
</tr>
<tr>
<td>40/2 (95/5)</td>
<td>273 ± 8</td>
<td>31.5 ± 0.4</td>
<td>58.8 ± 0.8</td>
<td>nanofibers</td>
<td>778 ± 111</td>
</tr>
<tr>
<td>40/3 (93/7)</td>
<td>628 ± 8</td>
<td>36.3 ± 0.7</td>
<td>58.9 ± 0.5</td>
<td>microfibers</td>
<td>1398 ± 117</td>
</tr>
<tr>
<td>50/0.5 (98/2)</td>
<td>240 ± 21</td>
<td>20.2 ± 1.1</td>
<td>58.5 ± 0.4</td>
<td>nanofibers</td>
<td>725 ± 123.8</td>
</tr>
<tr>
<td>60/0.1 (&gt;99%CD)</td>
<td>359 ± 25</td>
<td>8.3 ± 0.3</td>
<td>58.4 ± 0.9</td>
<td>spindle defects</td>
<td>1325 ± 515.2</td>
</tr>
<tr>
<td>70/0</td>
<td>3250 ± 45</td>
<td>6.2 ± 0.4</td>
<td>58.0 ± 0.8</td>
<td>nanofibers</td>
<td>986.7 ± 117.2</td>
</tr>
</tbody>
</table>

Table 3.2: Summary of results from entanglement analysis done by fitting data presented in Figure 3.3a.

<table>
<thead>
<tr>
<th>Solution</th>
<th>Semi-dilute unentangled slope</th>
<th>Semi-dilute entangled slope</th>
<th>Entanglement Concentration(Ce)</th>
<th>Concentration at onset of defect free fibers</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVA</td>
<td>~ 1.25</td>
<td>~ 3.8</td>
<td>~ 2.5</td>
<td>~ 6</td>
</tr>
<tr>
<td>20%HβCD/PVA</td>
<td>~ 0.8</td>
<td>~ 3.2</td>
<td>~ 1.7</td>
<td>~ 4</td>
</tr>
<tr>
<td>30%HβCD/PVA</td>
<td>~ 0.5</td>
<td>~ 2.7</td>
<td>~ 1.1</td>
<td>~ 3</td>
</tr>
<tr>
<td>40%HβCD/PVA</td>
<td>~ 0.4</td>
<td>~ 2.3</td>
<td>~ 0.8</td>
<td>~ 2</td>
</tr>
</tbody>
</table>
Table 3.3: DSC results for samples that contained crystallinity during the first heating scan.

<table>
<thead>
<tr>
<th>Sample (fiber blend)</th>
<th>PVA</th>
<th>30/70 PVA/HPβCD</th>
<th>50/50 PVA/HPβCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_m$ ($^\circ$C)</td>
<td>192</td>
<td>188</td>
<td>183</td>
</tr>
<tr>
<td>$\Delta H$ (J/g)</td>
<td>49.7 ± 0.7</td>
<td>32.9 ± 0.9</td>
<td>26.2 ± 1.0</td>
</tr>
<tr>
<td>Degree of Crystallinity (%)</td>
<td>30.8 ± 0.5</td>
<td>20.5 ± 0.6</td>
<td>16.3 ± 0.6</td>
</tr>
</tbody>
</table>
CHAPTER 4

Drug loaded Submicron Fibers Containing Cyclodextrins: Toward Rapid Dissolution/Release Membranes
Drug loaded Submicron Fibers Containing Cyclodextrins: Toward Rapid Dissolution/Release Membranes

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4.1 Introduction

Electrospinning is a practical and simple method for producing nanofibers that has gained much attention over the past few decades. This technique has been used to produce functional nanofibers from various polymers, polymer blends, composites, ceramics etc. The resulting electrospun nonwoven fiber mats possess a high surface to volume ratio and a high degree of porosity along with small pore sizes. These features render them immensely useful in a host of applications including medical devices, filtration devices, tissue scaffolds, protective clothing and reinforced composites.

Incorporating cyclodextrins into nanofibers creates an interesting opportunity for producing functional materials. Cyclodextrins (CDs) are ring-shaped oligosaccharides possessing a hydrophobic cavity and a hydrophilic exterior which imparts in them solubility in water. There are three main types of naturally occurring cyclodextrins namely α-, β-, and

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γ- which have 6, 7 and 8 member rings, respectively. Owing to their hydrophobic interior, cyclodextrin molecules can form noncovalent host-guest interactions which allow for complexation with poorly water soluble (PWS) small molecules and macromolecules\textsuperscript{11-15}. The complexation efficiency and stability between the host and guest depend on factors such as shape/size and specific functionalities that create binding forces with the CDs via hydrophobic interactions, van der Waals, and electrostatic forces\textsuperscript{16}.

Polymer nanofibers and CDs both find uses in the pharmaceutical field for drug delivery and combining them provides an exciting opportunity for this purpose. Nanofibers have been studied for both rapid and controlled release of drugs administered either transdermally or orally and is the subject of several reviews and a number of patents\textsuperscript{3, 17-20}. Electrospinning is of particular interest for drug delivery systems due to the ability to produce nanoparticulate drug-embedded nanofibers that can enhance the dissolution of PWS. Kenawy was the first to report on the use of nanofibers for drug delivery, studying the release of tetracycline hydrochloride from poly (ethylene-co-vinylacetate), poly (lactic acid), and blends thereof\textsuperscript{3}. Moreover, these systems could be designed to provide a range of dissolution rates (rapid, sustained, immediate, delayed, modified, etc.)\textsuperscript{1, 21}.

Fast dissolving/disintegrating drug delivery membranes (FDDM) are gaining attention for their applications in geriatric and pediatric patient care. For patients with difficulty swallowing or with the inability to produce sufficient saliva, a fast dissolving/disintegrating membrane to deliver drugs would be very useful\textsuperscript{22, 23}. FDDMs have
been made by various methods; however, nanofibers present several advantages such as extraordinary surface area to mass ratio and porous structure which facilitates rapid dissolution and the ability to distribute the drugs either in amorphous or nanocrystalline form. It has been reported that transforming PWS drugs into their amorphous or nanocrystalline morphology can potentially increase their dissolution rates. Yu et al. reported the first such use by electrospinning ibuprofen loaded PVP filaments and illustrated the rapid release (<15s) capabilities of nonwoven nanofiber mats.$^{22}$

The ability to electrospin neat chemically modified CDs and potentially tailor fiber composition and size by adding various amounts of a well-studied electrospinnable polymer (PVA) could be of great interest. Herein, we study the ability to load these blended fibers with ketoprofen, a model, PWS, non-steroidal anti-inflammatory drug (NSAID). The effects of adding ketoprofen on the electrospun fiber formation is also examined. The high water solubility of the fiber matrix materials combined with the high surface area of nano-scale fibers facilitates the delivery of the ketoprofen to create FDDMs with various dissolution rates that is dependent on fiber composition. HPβCD appears to be an ideal candidate due to its ability to complex with a wide range of drugs and its extraordinary water solubility. Moreover, cyclodextrins have already been used in some tablet formulations for FDDMs to provide taste-masking and enhanced bioavailability for patients.$^{12,23-26}$
4.2 Materials and Methods

Polyvinyl alcohol was purchased from Sigma-Aldrich (Mowiol 40-88\textsuperscript{®} (205,000 Da) and Hydroxypropyl-\(\beta\)-cyclodextrin was purchased from CTD, Inc (High Springs, Fl, technical grade, product code THPB-T) and were used without further purification. The average hydrolysis for this PVA is 88\%, meaning 12\% of the acetyl groups remain due to its production from vinyl acetate. The purity of THPB-T grade HP\(\beta\)CD is 91.2\%, and includes the presence of impurities such as water (3.4\%), propylene glycol (<5.0\%) and unsubstituted \(\beta\)-CD (<1.0\%). The average degree of substitution for this derivative was 5.6 (computed mol. wt.-1460). All solutions were made with deionized water.

The HP\(\beta\)CD and PVA solutions were made by adding the respective amounts of CD with supplemental water and allowed to mix in a shaker bath overnight at 35°C and 60 °C, respectively, in order to expedite dissolution. All solutions were stored in a refrigerator when not in use to prevent any degradation. Different blend ratios were made by adding various amounts of these stock solutions together as needed and then were mixed at 35 °C yielding homogenous solutions (displaying no turbidity).

All rheological experiments were performed at 25 °C in a TA Instruments AR-2000 stress controlled rheometer using cone and plate geometry. All rheological measurements were performed in triplicate to ensure reproducibility within ±5\%. Calorimetry studies were done on the HP\(\beta\)CD solutions using a TA instruments\textsuperscript{®} Q2000 Differential Scanning Calorimeter. Each sample (8-12 mg) was loaded into an aluminum pan and crimped. The
samples were ramped from room temperature to 250 °C, held isothermally for 5 min, then ramped back to room temperature, and finally ramped back to 250 °C for a second heating, the ramp rate used was 10 °C/min. The glass transition temperature was determined from the inflection point of the specific heat capacity of the second scan.

The electrospinning setup consisted of an aluminum collector plate, a precision syringe pump (Harvard Apparatus, Holliston, MA), and a high-voltage power supply (Gamma High Voltage Research, model D-ES30 PN/M692 with a positive polarity). The syringe pump controlled the flow of polymer solution to a metallic needle (22G) which was connected to the positive electrode of the power supply. The collector plate was grounded, and the fibers were collected on an aluminum foil wrapped on the collector plate. The tip-to-collector distance and solution flow rate were fixed at 12 cm and 0.5 mL/h, respectively, and the applied voltage ranged between 5 and 11 kV. The electrospun fibers obtained were gold-sputtered, and SEM measurements were obtained on a Hitachi S-3200 or FEI XL30 scanning electron microscope. The average fiber diameter was determined by measuring fiber diameters of at least 100 individual fibers from multiple SEM images using ImageJ software provided by NIH.

Fourier transform infrared spectroscopy (FTIR) studies were performed by a Nicolet 6700 FTIR spectroscope (Thermo Electron Corp) (Infrared spectra (400-4000 cm-1) and the XRD studies were carried out using a Philips X’Pert PRO MRD HR XRD System.
For the dissolution studies approximately 5 mg of electrospun mat was cut into squares. The mats were then dropped into a beaker containing 25 mL of water and the dissolution was monitored by videotaping with a Canon EOS SLR Rebel SR1 in high resolution mode.

The concentration of ketoprofen in the electrospinning solutions was determined by UV–Vis absorbance spectrophotometry (Jasco V550). A calibration curve for ketoprofen in water was constructed to with less than a 3% COV (coefficient of variation). The presence of PVA and HPβCD was found not to affect the UV absorbance spectrum for ketoprofen. The concentration of the solutions was measured at a wavelength of 260 nm.

4.3 Results and Discussion

4.3.1 Ketoprofen Dissolution

Drug-cyclodextrin phase-solubility diagrams, that show the relationship between drug solubility and cyclodextrin (ligand) concentration in solutions, fall into two main categories, A- and B-types. A-type curves are indicative of the formation of soluble inclusion complexes while B-type behavior is suggestive of the formation of inclusion complexes with poor solubility. Though β-cyclodextrin often gives rise to B-type curves due to the poor water solubility of the ligand itself, chemically modified CDs including HPβCD usually produce soluble complexes (i.e., A-type systems). A_L systems show a linear relationship between drug and the ligand, while A_P and A_N show a positive and negative deviation from this
behavior, respectively. Most pharmaceutical studies measure concentrations in molarity, however, we report concentration in wt% (w/w) due to the large changes in specific gravity encountered with high HPβCD concentrations (up to 70 wt%). Moreover, these solutions become difficult to handle due to high viscosities making volumetric measurements inaccurate. Therefore, instead of a molarity comparison, the relationship between the moles of ketoprofen and moles of HPβCD in aqueous solutions is shown in Figure 4.1. The phase-solubility relationship, at the concentrations studied here, shows an A_P-type behavior. It has been demonstrated that the phase-solubility relationship of ketoprofen and HPβCD is an A_L-type relationship at concentrations up to 100 mmol aqueous solutions which is equivalent to approximately 15 wt% HPβCD. However, in this study, HPβCD concentrations exceed this value and are as high as 70 wt%.

Additionally, it is important to examine the stoichiometry of ketoprofen to HPβCD. A-type diagrams are first order with respect to the cyclodextrin (L) and may be first or higher order with respect to the drug. If the slope of an A_L-type system is greater than one, higher order complexes are indicated. However, a slope of less than one does not necessarily exclude higher order complexation, though 1:1 complexation is usually assumed in the absence of other information. A_P-type systems imitate the formation of higher order complexes with respect to the ligand at higher ligand concentration. Mura et al. suggests that ketoprofen:HPβCD follows a 1:1 stoichiometry in their concentration range studied, however it appears that, in the concentration ranges examined here, the phase-solubility plot
points to a 1:2 ketoprofen:HPβCD stoichiometry with a change to a higher degree of complexation above 0.003 moles of cyclodextrin in solution. Based on these data, it would then be advantageous to have the largest amount of HPβCD loading possible in order to achieve the highest drug loadings. To our knowledge, this is the first study in which ketoprofen aqueous phase-solubility has been examined at this HPβCD concentration range.

Furthermore, the solubility of ketoprofen in neat aqueous HPβCD solution may help elucidate the impact of the addition of PVA to the solutions. A summary of the drug loadings for electrospun fibers of PVA, HPβCD and PVA/HPβCD bicomponent fibers is shown in Table 4.1. The lower solubility of PVA (~12 wt%) when compared to that of HPβCD (~75 wt%) relegates PVA to an electrospinning aid while HPβCD is to be considered the solubilizing agent. As expected, the fibers produced from solutions containing larger amounts of HPβCD have higher drug loadings. However, unlike other water soluble polymer such as PVP, hydroxymethyl cellulose and PEO which have shown a synergistic effect on the complexation of CDs with PWS drugs, PVA does not appear to aid in the complexation of HPβCD. For comparison, solutions of 30% HPβCD and 30% HPβCD/0.5% PVA (Table 4.2) were made in order to determine drug loading capabilities. A reduction in ketoprofen loading is seen with the addition of increasing amounts of PVA to a base of 30% HPβCD. A reduction in drug loading suggests PVA may actually have an anti-synergistic effect in the complexation of ketoprofen with HPβCD. In our previous work (Chapter 3) we suggested that PVA was not complexing (threading) the HPβCD in the
blended solutions. However, complexation, albeit small, was not completely ruled out and could be a contributing factor to the reduction of drug complexation with HPβCD. This reduction could be a result of blockage due to threading of the CD’s core. Another possible explanation is that the addition of PVA may be shielding the drug from complexation with HPβCD through other mechanisms beside threading or possibly even extending the complexation equilibrium times well passed those considered here. These are interesting results and are outside the scope of this study.

4.3.2 Electrospinning of Drug Loaded Fibers

SEM micrographs of fibers electrospun from aqueous solutions of PVA, HPβCD, and HPβCD/ PVA blends are shown in Figure 4.2 (a-f). The fibers are continuous, defect free, and possess a well-controlled fiber diameter. The neat PVA fibers had the smallest diameters while the neat HPβCD fibers possessed the largest fiber diameters, matching our findings from Chapter 3. These blends were chosen based on the criteria that certain blend ratios (0/100, 30/70, 50/50, 70/30, 90/10, and 100/0 HPβCD/ PVA) were achieved (dissolved in water to form a clear solution) and defect free fibers were produced from these solution blends. Therefore, neither the overall solute nor the individual components were held constant. It was found that a high concentration of HPβCD (70 wt%) was needed to create defect free fibers, while a relatively lower concentration of PVA (6 wt%) was needed to electrospin smooth PVA fibers. Therefore, blends containing more PVA have a lower amount of overall spinning material (HPβCD and PVA) than fibers that contain mostly
HPβCD, which need a much higher overall concentration of spinning material to obtain fibers. Table 4.1 lists the concentrations (in wt%) of each component in aqueous electrospinning solutions and the corresponding fiber blend ratio as it pertains to PVA and HPβCD only.

Once the above criteria for spinning smooth fibers were met, the effect of loading ketoprofen into the aqueous spinning solutions was studied. Micrographs of fibers electrospun from the ketoprofen loaded solutions are shown in Figure 4.3 (a-f). These fibers are also continuous and defect free much like their corresponding electrospun fibers without ketoprofen (shown in Fig. 4.2 (a-f)). Furthermore, there are no signs of phase separation in the form of drug particles as was seen by Yu et al in ibuprofen loaded PVP fibers. This indicates that the drug is stable in solution and does not agglomerate during the electrospinning process and is assumed to be well distributed throughout the fibers.

It is well known that surface tension, viscosity, and electrical conductivity (hereafter will be referred to only as conductivity) play an important role in the final fiber formation. Surface tension is the primary opposing force to the high electric field formed during the electrospinning process. Therefore, holding all other conditions equal, lowering this value is ideal in producing smooth continuous fibers. For a polymer solution, the viscosity is usually indicative of the interactions between the polymer and solvent molecules. Therefore, the magnitude of the viscosity should be such that it produces a continuous, cohesive jet that can withstand stretching under the pull of a high electric field. The values for the surface
tension and viscosity for both neat and ketoprofen loaded bicomponent spinning solutions are shown in Table 4.1. The surface tension for the ketoprofen loaded fibers appeared to be slightly lower than the values measured for the neat bicomponent solutions at lower HPβCD loadings. This reduction in surface tension could be due to the increased number of free drug molecules present in solutions with lower HPβCD content. Solutions with higher concentrations of HPβCD showed no change in surface tension with the addition of drug owing to its ability to complex with any drug present in solution. Regardless, these are only minute changes and therefore are not considered to be an important factor. Furthermore, the viscosity of the neat and drug loaded bicomponent solutions show no discernable trend and were also considered to be insignificant in dictating the final fiber morphologies relative to the neat bicomponent fibers. The factor that had the highest degree of change was the conductivity. Figure 4.4a shows the effect of loading ketoprofen into the electrospinning solutions on the conductivity. The solution conductivities are generally larger for drug loaded solutions and become prominent at higher ketoprofen concentrations (see Table 4.2). This increase in conductivity (Fig. 4.3a) is reflected in a decrease in fiber diameters (Fig 4.3b). A noteworthy change (in conductivity and fiber diameter) is seen only in the case where there is a significant increase (3X increase for ketoprofen loaded solution) in conductivity due to the addition of ketoprofen (namely 30/3 HPβCD/PVA). Overall, the addition of ketoprofen has only a small effect on the fiber diameter and no noticeable effect on morphology. It should be noted that the effects of the neat bicomponent blend ratios have already been discussed in our previous work (Chapter 3) and are not discussed further here.
4.3.3 Properties of the Electrospun Fibers

Infrared spectra in the C=O stretching region of ketoprofen (acid and ketonic carbonyl group bands at 1700 and 1660 cm\(^{-1}\)) and respective solids (HP\(\beta\)CD and PVA) is shown in Figure 4.5\(^{27}\). The characteristic acid carbonyl stretching band of the pure drug is prominent in all cases where drug loaded solutions were electrospun and is shifted to a higher frequency (1720 cm\(^{-1}\)) in the electrospun products. This spectral shift can be attributed to the breakdown of the intermolecular hydrogen bonds of the drug crystals and formation of a monomeric dispersion of drug\(^{29}\). It is also a consequence of the interaction of ketoprofen with the HP\(\beta\)CDs, resulting from the inclusion of the drug monomer into the hydrophobic cavity of the carrier\(^{27,30}\).

We also examined by DSC and XRD to confirm that ketoprofen is amorphously distributed. The DSC thermograms and XRD diffraction patterns for neat and ketoprofen loaded fibers are presented in Figure 4.6a and Figure 4.6b, respectively. A sharp melting peak is present for the neat ketoprofen solid at approximately 94 °C, indicating that ketoprofen is crystalline in nature. However, for the drug loaded fibers, no crystalline melting peak is present, signifying that the drug is amorphously distributed in the fiber matrix owing to its complexation with the CD's core. Moreover, the diffraction patterns for the neat drug designate a highly crystalline structure, while the patterns associated with drug loaded fibers point toward ketoprofen being present in a nanocrystalline or amorphous state. For fast dissolving drug delivery membranes it is important to make certain that the drug is
molecularly distributed throughout the fiber matrix to assure rapid dissolution and total release as the fiber matrix disintegrates and dissolves in the delivery medium. Crystalline drugs would be resistant to dissolution and can cause delayed release to the body.

4.3.4 Rapid Dissolution of Drug Loaded Fibers

The dissolution times were studied by videotaping the drug-loaded fiber mats as they made contact with the surface of liquid water and stills were captured at different times after contact. Stills were taken from the time at which the fiber mat landed on the water’s surface (t = 0s) and in fractions of seconds after. When fiber mats of ketoprofen loaded HPβCD (0% PVA) were put into water, they disintegrated and dissolved almost immediately as each part of the mat made contact with the water surface. Stills of the mats dissolution, at different times after water contact, are shown in Figure 4.7 (a-d). No gel was detectable by the naked eye after 0.207s (fig 4.7d). These experiments were repeated multiple times and it was found that there was no discernable difference in dissolution times with respect to the resolution of the camera used. That is, the mat was totally disintegrated and dissolved by the frame recorded at approximately 0.207s each time for HPβCD membranes. This time is extremely fast in comparison to PVP membranes loaded with Ibuprofen (~ 8s) studied by Yu et al due to the extraordinary water solubility of HPβCD and the large surface areas inherent in submicron fibers. The rapid dissolution combined with the other merits of HPβCD (including increased bioavailability, taste masking, and low toxicity) suggest that this
system is a good candidate for rapid dissolution/delivery in aqueous environments (e.g., mouth)\textsuperscript{23}.

The addition of PVA slowed the dissolution of the membranes owing to its lower solubility in water when compared to HPβCD. A summary of dissolution times is given in Table 4.3. The dissolution times were chosen as the times in which no discernable gel was left on the water surface. The increase in dissolution times appear to be directly proportional to the amount of PVA in the fiber with the exception of PVA only ketoprofen loaded fibers. This could be due to the PVA fibers possessing the smallest fiber diameter and reveals a balance between solubility and fiber diameter with respect to dissolution times.

Because the ketoprofen was shown to be amorphously distributed within the fiber, it is believed that the total disintegration and dissolution of the fibers led to the complete release of the drug contained within. These results indicate once more that it is advantageous to create fibers with the highest possible loadings of HPβCD in order to release the drug in the shortest time.

4.4 Conclusions

Herein, we report the first time that CDs have been electrospun as excipients with and without a carrier polymer (PVA). Although, it was possible to electrospin HPβCD alone, PVA was used to facilitate electrospinning of various blended fibers to allow tailoring of blend ratios and fiber diameters. The electrospinning solutions were loaded with a model
NSAID, ketoprofen, and the solubility was measured. It was found that PVA actually diminished the ability of HPβCD to complex and solubilize ketoprofen when compared to neat HPβCD solutions. Furthermore, the effect of the addition of ketoprofen on the electrospinning process was studied. The conductivity of the solutions tended to rise upon the addition of ketoprofen resulting in a slight decrease in average fiber diameter.

Smooth, continuous fibers were achieved by electrospinning these drug loaded solutions in all cases. FTIR results showed that the drug was monomerically distributed throughout the fiber matrix due to a breakdown of interactions as the ketoprofen molecules were complexed within the HPβCD core. DSC thermograms and X-ray diffraction patterns confirmed this finding as no crystallinity was detected and therefore the drug was distributed in its amorphous form.

The time for dissolution of the fibers was also determined. It was found that fibers containing only HPβCD and ketoprofen disintegrated in approximately 0.207 seconds and the addition of PVA generally increased the dissolution times. Overall, to achieve the fastest drug release and the maximum drug loading, it was determined that fibers with the highest loading of HPβCD possible have to be fabricated because of HPbCD’s extraordinary water solubility and ability to solubilize drug molecules.
4.5 References


Figure 4.1: Phase-solubility relationship between ketoprofen and HPβCD with respect to total moles in aqueous solutions.
Figure 4.2: SEM micrographs of electrospun HPβCD/ PVA bicomponent fibers: a) 0/100 b) 30/70, c) 50/50, d) 70/30, e) 90/10, and f) 100/0 (HPβCD/ PVA).
Figure 4.3: SEM micrographs of electrospun PVA/HPβCD bicomponent fibers containing ketoprofen: a) 0/100 b) 30/70, c) 50/50, d) 70/30, e) 90/10, and f) 100/0 (HPβCD/PVA).
Figure 4.4: The a) conductivity of the electrospinning solutions and b) average fiber diameter of fibers produced as a function of HPβCD% (w/w total solute) of neat and ketoprofen loaded fibers.

Figure 4.5: Infrared spectrum of the carbonyl (C=O) stretching region for ketoprofen for neat and drug loaded fibers of HPβCD and HPβCD/PVA bicomponent fibers.
Figure 4.6: The a) DSC thermograms and b) X-ray diffraction patterns for ketoprofen and the other solids in the system as specified.

Figure 4.7: The evolution of the dissolution of ketoprofen loaded HPβCD fibers with respect to time.
Table 4.1: Summary of some solution parameters for aqueous electrospinning solutions containing PVA, HPβCD and indicated blends.

<table>
<thead>
<tr>
<th>Blend</th>
<th>Viscosity (cP)</th>
<th>Surface Tension (dynes/cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(HPβCD/PVA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/6 (0/100)</td>
<td>185 ± 7</td>
<td>52.7 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>192 ± 8</td>
<td>51.0 ± 0.6</td>
</tr>
<tr>
<td>2.57/6 (30/70)</td>
<td>195 ± 9</td>
<td>53.5 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>212 ± 11</td>
<td>51.7 ± 0.7</td>
</tr>
<tr>
<td>6/6 (50/50)</td>
<td>344 ± 10</td>
<td>54.2 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>325 ± 11</td>
<td>52.3 ± 0.6</td>
</tr>
<tr>
<td>14/6 (70/30)</td>
<td>554 ± 16</td>
<td>54.5 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>524 ± 12</td>
<td>53.7 ± 0.9</td>
</tr>
<tr>
<td>30/0 (100/0)</td>
<td>213 ± 12</td>
<td>58.6 ± 0.7</td>
</tr>
<tr>
<td></td>
<td>221 ± 12</td>
<td>58.6 ± 0.5</td>
</tr>
<tr>
<td>70/0 (100/0)</td>
<td>3250 ± 45</td>
<td>58.0 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>3451 ± 34</td>
<td>57.2 ± 0.8</td>
</tr>
</tbody>
</table>

Table 4.2: Drug loading in electrospun fibers of PVA, HPβCD and HPβCD/PVA blend ratios in wt% (w/w) derived from UV spectra data. The highlighted values are for comparison only and were not electrospun. The first ratio represents the percent of each component in solution while the second ratio, in parenthesis, represents the final fiber ratio ignoring the amount of drug present.

<table>
<thead>
<tr>
<th>Blend</th>
<th>Drug loading (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/6 (0/100)</td>
<td>1.16 ± 0.09</td>
</tr>
<tr>
<td>2.57/6 (30/70)</td>
<td>2.38 ± 0.11</td>
</tr>
<tr>
<td>6/6 (50/50)</td>
<td>3.74 ± 0.12</td>
</tr>
<tr>
<td>14/6 (70/30)</td>
<td>5.01 ± 0.11</td>
</tr>
<tr>
<td>30/0 (100/0)</td>
<td>8.55 ± 0.10</td>
</tr>
<tr>
<td>30/0.5 (98/2)</td>
<td>8.25 ± 0.08</td>
</tr>
<tr>
<td>30/3 (90/10)</td>
<td>7.12 ± 0.15</td>
</tr>
<tr>
<td>70/0 (100/0)</td>
<td>11.12 ± 0.13</td>
</tr>
</tbody>
</table>
Table 4.3: Summary of dissolution times for drug loaded fibers for the blends studied. The time indicated was chosen based on the first point at which gels were no longer visible to the naked eye.

<table>
<thead>
<tr>
<th>Blend (CD/PVA)</th>
<th>Dissolution time (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0/100</td>
<td>462 ± 25</td>
</tr>
<tr>
<td>30/70</td>
<td>520 ± 32</td>
</tr>
<tr>
<td>50/50</td>
<td>415 ± 28</td>
</tr>
<tr>
<td>70/30</td>
<td>180 ± 19</td>
</tr>
<tr>
<td>90/10</td>
<td>10 ± 1.5</td>
</tr>
<tr>
<td>100/0</td>
<td>~0.207</td>
</tr>
</tbody>
</table>
CHAPTER 5

Porous Electrospun Nanofibers Using Oligosaccharides as a Porogen
Porous Electrospun Nanofibers Using Oligosaccharides as a Porogen

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5.1 Introduction

Electrospun nanofibers can have potentially a wide array of applications that include filters, scaffolds, membranes, biological sensors, transport media, light weight reinforcement, and coatings. In these applications, the performance of the nanofibers could be greatly improved by modifying the textural properties of the fibers, for instance by increasing surface area and porosity. Hence, a number of studies have reported the generation of porous fibers using various schemes. Researchers have reported that by using a high-vapor pressure solvent in the electrospinning process, fibers with unusual surface porous structures could be achieved. The regular surface pore morphology is thought to be generated by rapid phase separation during electrospinning, wherein the solvent rich regions in the elongated polymer jet are transformed into pores after solvent evaporation and subsequent rapid polymer solidification.

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Dayal and coworkers\textsuperscript{12} employed a similar approach to investigate experimentally and theoretically the pore structure formation in electrospun porous fibers using volatile solvents. They spun fibers from amorphous polymer solutions of poly(methyl methacrylate)/methylene chloride and poly(styrene)/tetrahydrofuran and from their work they found that porous fiber formation is favored if the polymer/solvent system is partially miscible showing an upper critical solution temperature (UCST) behavior at the electrospinning temperature. The pore size is determined to depend on diverse factors which include surface energy and solvent evaporation rates. There are four phase separation mechanisms that are envisaged to produce porous membranes: 1) thermally induced phase separation (TIPS), 2) immersion precipitation, 3) air-casting of the polymer solution, and 4) precipitation from the vapor phase\textsuperscript{9}. According to Megelski et al., the driving force behind phase separation is thermodynamic instability. Solvent loss, temperature decrease or increase in nonsolvent (e.g. moisture) triggers a solution toward thermodynamic instability during the electrospinning process, which subsequently constrains phase separation, eventually causing pore formation.

Electrospinning of sol-gel solutions of inorganic materials with surfactants can also produce porous fibers\textsuperscript{13}. McCann and coworkers showed that by using a coaxial spinneret with miscible solvents and immiscible polymers, highly porous fibers could be obtained by selective dissolution and calcination of the composite fibers\textsuperscript{14}. They also produced porous polystyrene, polyacrylonitrile, and polyvinylidene fluoride fibers by immersing the collector in a bath of liquid nitrogen followed by drying in vacuum\textsuperscript{15}. The porous fibers were obtained
through thermally induced phase separation between the solvent rich and solvent poor regions in the fiber during electrospinning.

Several research groups have also produced porous fibers by electrospinning polymer blends, followed by selective removal of one component\textsuperscript{14, 16}. For example, Bognitzki and coworkers\textsuperscript{10} synthesized porous fibers of polylactic acid (PLA) and polyvinyl pyrrolidone (PVP) by electrospinning a PLA/PVP blend solution. When the resulting PLA/PVP blend nanofibers were immersed in water, the PVP was selectively extracted obtaining porous PLA nanofibers. Similarly, Zhang et al. (two different groups) used the concept of phase separation with electrospinning to generate polyacrylonitrile (PAN)-poly(ethylene oxide) (PEO) (15-50 wt.% of PEO in PAN)\textsuperscript{17} and PAN-PVP (20-56 wt % of PVP in PAN)\textsuperscript{18} bicomponent fibers. The nanopores were generated by the dissolution of the phase separated PEO and PVP domains in water and the selective removal of the PEO and PVP component was confirmed by Fourier Transform Infrared Spectroscopy (FTIR) and differential scanning calorimetry (DSC). However, they found surprisingly that the removal of one component increased the average fiber diameters. Although viable in principle, nanopore generation via this method is time intensive due to the slow solubilization of most polymers, and in some cases complete removal of the unwanted component may not be possible.

A modification to the use of volatile solvents to create porous fibers is the tuning of the relative humidity during electrospinning\textsuperscript{11, 19}. This approach allowed the generation of pores concentrated either on the surface or on the interior of the fibers depending on the
miscibility/immiscibility of water with the electrospinning solvent. Surface porosity was formed when water is miscible with the solvent\textsuperscript{11} while interior porosity was favored when water is immiscible with the solvent\textsuperscript{19}. Pore density for both methodologies increased with humidity. Recently, Lin et al. reported the direct fabrication of nanoporous polystyrene electrospun fibers using a mixture of volatile (THF) and non-volatile (DMF) solvents as the electrospinning solvent system\textsuperscript{20}. The porous structures were modulated by varying the polymer concentration and the mixed solvent ratios. Another new approach utilized polymer colloids as porogen mixed in PAN solution to prepare porous carbon fibers by carbonization of electrospun PAN-polymer colloid solution\textsuperscript{21}. Since the average size of the polymer colloids were 300 nm, carbonization of the electrospun fibers left interconnected macropores inside the resulting carbon fibers with mesoscale openings in the fiber surfaces.

Addition of salts into the electrospinning system has been shown to control the fiber structure and properties due to increased electrical conductivity in the electrospinning polymer solution\textsuperscript{22}. Recently, we previously reported a novel approach in producing porous nylon-6 fibers by electrospinning a Lewis acid-base complexation of gallium trichloride (GaCl\textsubscript{3}) and nylon-6 followed by GaCl\textsubscript{3} water extraction\textsuperscript{23}. While the average fiber diameter remains effectively the same after salt removal, the average surface area increased by more than a factor of 6 for the regenerated fibers. Our study showed a facile approach with the dual use of a metal salt (Lewis acid) to both facilitate fiber formation by an interim removal of nylon interchain interactions and to act as a porogen to obtain fibers via electrospinning.
For this study, we report the use of hydroxypropyl beta-cyclodextrin (HBbCD), an oligosaccharide as a porogen to generate porous PAN electrospun nanofibers. We established that HBbCD to be readily soluble in DMF (solvent for PAN) which allowed the formation of a clear, homogenous polymer solution for electrospinning. We envision that since HBbCD is smaller in size than a typical polymer, it will not disrupt molecular entanglement of the electrospinning polymer chains in solution which is necessary for fiber formation, and it will also facilitate its easier removal from the as spun fibers during removal/extraction by water treatment. Moreover, because of its smaller size and its capability to interact with either a polar or nonpolar functional groups in the electrospinning polymer, the formation of larger aggregates during phase separation, as maybe true with salts as porogen (i.e. the formation of salt crystals), we would expect smaller pore sizes, and therefore higher surface areas, would be achieved in the resulting porous fibers.

In addition, since PAN is a common precursor for carbon fibers we also investigate the results of carbonizing both as-spun fibers and porous (water treated) fibers. The degradation temperature of HPβCD is close to the temperature at which PAN can be stabilized before eventually carbonizing. This should allow for PAN to stabilize around the porogen and lock in the porous morphology before eventually pyrolyzing the remaining cyclodextrins, producing extraordinarily high surface area microporous carbon fibers. We demonstrate that fibers carbonized after the removal of the porogen showed similar surface area and pore volumes to that of carbon fibers made from neat PAN electrospun fibers.
5.2 Experimental Section

HBbCD was purchased from CTD, Inc (High Springs, Fl, technical grade, product code THPB-T). The purity of this grade is 91.2% with the impurities as water (3.4%), propylene glycol (<5.0%) and unsubstituted β-CD (<1.0%). The average degree of substitution for this derivative was 5.6 (computed mol. wt. 1460). PAN (MW = 150 000) and solvent N,N-dimethylformamide (DMF) were obtained from Aldrich Chemical Company Inc (USA). All these reagents were used without further purification. The overall scheme of the fabrication of porous PAN and carbon nanofibers using HPβCD as porogen is presented in Figure 5.1. Typically, predetermined amounts of PAN and HPβCD are mixed in DMF in separate vials and heated at 60 °C to expedite dissolution. The mixtures are stirred for three to four hours to ensure complete dissolution, after which the two solutions are combined in certain ratios and stirred for several more hours. After the dissolution, the resulting solution is left for an hour to cool and eliminate any air bubbles and is subsequently electrospun or analyzed further.

Rheological analysis was performed at 25 °C using a TA Instruments AR-G2 stress-controlled rheometer fitted with a 40 mm, 2° cone and plate geometry. Steady shear and dynamic experiments were performed on each sample. To ensure uniform solution conditioning, a preshear of 1 Pa for 60 seconds was applied, followed by a rest period of 120 seconds. A dynamic stress sweep was performed in order to identify the linear viscoelastic
regime, which was used to perform the frequency sweep. Zero-shear viscosity was determined from the steady shear experiments. Each experiment was performed at least twice, which were reproducible within ±5%. Surface tension was measured using a Whilhelmy plate (Sigma 70, KSV Instruments Ltd.)\textsuperscript{24}, and solution conductivity was measured with a conductivity meter (Fisher Accument BASIC AB30) as described previously.

The design of the electrospinning setup was based on a point-plate configuration, using a precision syringe pump (Harvard Apparatus, Holliston, MA) and a high-voltage power supply (Gamma High Voltage Research, model D-ES30 PN/M692). Details of the apparatus have been previously described. Typically, a flow rate of 0.5 mL/hr, a tip to collector distance of 15 cm, and a voltage of 6-12 kV was used.

Stabilization and carbonization were carried out in a ceramic tube furnace in a similar fashion to Ji \textit{et al}\textsuperscript{25}. The fibers were loaded into the center of the tube and sealed with rubber grommets at each cool end of the furnace to ensure an air-tight seal. The furnace was heated at a rate of 5 °C/min to 280 °C and held isothermal for 5.5 hours all under an air environment (UHP) to stabilize the fibers. Then the furnace was heated at 2 °C/min to 800 °C and held isothermal for 1 hour to pyrolize the fibers.

BET surface areas were determined from N\textsubscript{2} adsorption isotherm data collected at 77 K (Autosorb-1, Quantachrome Corp., Boynton Beach, FL). Prior to analysis, adsorbent samples were outgassed for 1 h at 298 K. BET surface areas were determined from 10-point
adsorption isotherms that were completed with at least 0.2 g sample in the 0.05−0.3 relative pressure range. A glass rod was used during the analysis to decrease the void volume of the sample holder. Pore size distributions were determined by conducting N₂ adsorption experiments constructed from 44 data points in the relative pressure range of 0.05−1 using a sample mass of 1.0 g of adsorbent. A glass filler rod was inserted into the sample holder to minimize the void volume in the sample holder during the analysis. Mesopore volume and pore size distribution were computed from N₂ adsorption isotherm data using the density functional theory (DFT) with the N2_carb1.gai kernel (PC software version 1.51, Quantachrome, Boynton Beach, FL). In addition, the mesopore volume was computed using the Barrett, Joyner, and Halenda (BJH) and DFT methods. The BJH method is commonly used to determine the volume and size distribution of mesopores (2−50 nm) and small macropores, and the DFT method is typically used to estimate the volume and size distribution of micropores (<2 nm) and small mesopores. The relative surface area, micropore volume and pore size distribution for the carbon fibers was analyzed using the DFT method and the HK (Horvath-Kawazoe) using adsorption data (CO₂ gas) by Micromeritics Corp. (Norcross, GA).

The morphology and size of the resulting electrospun nonwoven fiber mats were evaluated using scanning electron microscopy (SEM, FEI XL30). The electrospun fibers obtained for SEM analysis were gold-sputtered to prevent charging, except for the carbonized fibers where SEM analysis was done to neat carbonized fibers to prevent any distortion of the porous morphology. The average fiber diameter was determined by
measuring fiber diameters of individual fibers from multiple SEM images using RevolutionSEM™ software by 4Pi Analysis, Inc. and ImageJ software provided by the National Institute of Standards and Technology (NIST). The nanofibers were also characterized using transmission electron microscopy (TEM, FEI Tecnai G2 Twin). Samples for TEM analyses were deposited directly to TEM carbon-coated copper grids (Electron Microscopy Sciences and Ted Pella Inc.) fastened to the aluminum foil and removed from the collector plate after the electrospinning deposition. Differential scanning calorimetry (DSC) was performed on the electrospun nanofibers using TA instruments® Q2000 Differential Scanning Calorimeter. The XRD studies were carried out using a Philips X’Pert PRO MRD HR XRD System. Raman spectroscopy was done using a Horiba-Jobin Yvon LabRamHR VIS high resolution confocal Raman microscope system with 633 nm laser.

5.3 Results and Discussion

5.3.1 Electrospinning of PAN and PAN/HPβCD blends in DMF

PAN and HPβCD are soluble in DMF and form clear homogenous solutions at concentrations up to ~12% (w/w) and ~60% (w/w), respectively. It was found that a concentration of at least 7.5% PAN in DMF was necessary to electrospin defect free fibers. Therefore all solutions studied here contain 7.5% PAN as a baseline in order to ensure electrospinnability while allowing for the largest amount of HPβCD to be added without triggering any observed phase separation in the solutions. The blended solutions were tailored in order to achieve certain fiber compositions. For example, the 50/50 PAN/HPβCD
solutions and fibers discussed here were made from solutions containing 7.5% PAN and 7.5% HPβCD. It was found that solutions aimed at producing a 40/60 PAN/HPβCD were not easily electrospun as some phase separation was visually observed and needle clogging ensued. Therefore, 50/50 fiber blends were the maximum loading of HPβCD studied. All the solution blends studied here formed transparent and uniform solutions in DMF and remained stable throughout the electrospinning process.

Although PAN and HPβCD are miscible in solution they appear to phase separate upon evaporation of the solvent DMF. Additionally, while DMF is a good solvent for both species, water is a nonsolvent for PAN but a good solvent for HPβCD allowing for the removal of HPβCD during water soaking. To illustrate the phase separation, solution cast films made from DMF solutions of pure PAN and 50/50 PAN HPβCD were subjected to optical microscopy analysis. The resultant micrographs are presented in Figure 5.2. Fig. 5.2a shows the morphology of a pure PAN film that was soaked in water. The image shows that the film is smooth and without any discernable features. However, the as-cast film of the 50/50 blend (Fig 5.2b) results in a rough, undulating morphology likely due to phase separation during evaporation of the DMF solvent. After water soaking a rough, pitted morphology with nanoscale features (Fig 5.2c) are generated. This is indicative of phase separation occurring in the films as the removal of CD results in a porous interconnected structure.
Fibers were then electrospun from the PAN/HPβCD blended solutions to further investigate how this phenomenon translates to making highly porous fibers. As aforementioned, these solution blends that form homogenous solutions, largely defect free and continuous fibers were achievable for blends up to 50/50 PAN/CD in DMF. The morphology of the as-spun fibers is shown in Figure 5.3.

The bicomponent fibers were successfully prepared without evidence of beads or fusion that might indicate solution phase separation. In the electrospinning process, the solution viscosity, electrical conductivity (hereafter referred to as just conductivity) and surface tension have been found to be important in dictating the as-spun fiber morphology and diameter. In general, a viscous, electrically conductive solution with a low surface tension facilitates the production of defect free nanofibers\textsuperscript{26}. These important solution parameters are presented in Figure 5.4.

All the solutions tested were found to be newtonian with no evidence of shear thinning and their respective zero shear viscosities are presented in Fig 5.4a. The viscosity of a mixture has been shown to depend on the compatibility of the components in solution\textsuperscript{27}. The viscosity of the maximum amount of HPβCD in these solutions at a 50/50 blend, 7.5 wt% HPβCD in DMF alone has a zero-shear viscosity of approximately 3 cP. The disproportional increase in viscosity for the mixture shows a general increase with increasing HPβCD concentration owing to interactions between HPβCD and PAN resulting in a homogenous, miscible system. These interactions are due to the hydrogen bonding
capabilities of the hydroxyl groups of HPβCD and the nitrile groups on PAN akin to what Shin et. al. observed in their work with cellulosic blends with PAN\textsuperscript{28}.

Conductivity is another important parameter in the electrospinning process as it fundamentally requires the transfer of electric charge from the electrode to the droplet at the apex of the tip. Similar to our previous work with the PVA/HPβCD system, the conductivity of the PAN/HPβCD system generally decreases with an increase of HPβCD and is attributed to a reduction in mobility of the solvent. On the other hand, an increase in conductivity was observed for adding 7.5% PAN (47.5 ± 0.8 μS/cm) compared to DMF alone (2.2 ± 0.6 μS/cm) due to an increase in ionic groups.

Surface tension is the primary force that opposes coulombic repulsion and plays a role in the electrospinnability of a solution. It is often a combined effect of surface tension and viscosity that determines the window for which solutions can be electrospun\textsuperscript{29}. However, in our system the surface tension (Fig 5.4b) of the solutions were found to be independent of the amount of CD present. Therefore it is expected that viscosity is the dominant factor in determining the bicomponent fiber size and morphology. Figure 5.5 shows the evolution of fiber diameters with increasing HPβCD concentration.

The fiber diameter generally increases with an increase in HPβCD content to the solutions. The increase in fiber diameter is likely due to the increase in viscosity as seen in Fig. 5.4a where the trends in both plots closely map each other. Solution viscosity is
generally identified as the dominant variable that determines fiber diameter. Typically, increasing the viscosity of an electrospinning solution results in larger fiber diameter due to an increase in the resistance of the polymer jet to stretch under a high electric field\textsuperscript{30}. The reduction in conductivity could also give rise to larger fibers as in general, a decrease in the conductivity of the solution would bring about an increase in the fiber diameter given that the solutions would carry less charge and be not subjected to as high of stretching forces under the electric field\textsuperscript{26,31}.

5.3.2 Phase Separation in Bicomponent Fibers

As mentioned previously, it is important to ascertain that HP\(\beta\)CD is both incorporated in the as-spun fiber and that it can then be removed from the bicomponent fibers by water treatment to form a porous morphology. We refer to fibers that have been water treated and the HP\(\beta\)CD porogen removed as “regenerated fibers”. FTIR was used to detect the presence of HP\(\beta\)CD in the bicomponent fibers by monitoring the salient absorption bands from HP\(\beta\)CD at \(\sim 1030, \sim 1080,\) and \(\sim 1155\) cm\(^{-1}\) (due to coupled C-C/C-O stretching and antisymmetric stretching vibrations of the C-O-C glycosidic bridge)\textsuperscript{32}. As can be seen for both pure HP\(\beta\)CD and as-spun PAN/HP\(\beta\)CD mats in Figure 5.6, these absorption bands are present indicating the successful incorporation of HP\(\beta\)CD into the bicomponent fibers. The absorption spectra for the neat PAN fibers and the blends (both as-spun and regenerated) show the stretching –C≡N bond vibration at \(\sim 2245\) cm\(^{-1}\) and strong –C-H in-plane deformation vibration –CH\(_2\)- group at \(\sim 1450\) cm\(^{-1}\), both of which are characteristic of the
PAN polymer. The lack of influence of the two species on each other in the spectra of the as-spun 50/50 PAN/HPβCD fibers indicates an absence in intermolecular interactions and implies phase separation between PAN and HPβCD in the bicomponent fibers. The spectra for the as-spun PAN and regenerated blend are almost identical with no signature peaks from HPβCD. This confirms that by soaking the as-spun bicomponent fibers in water, most, if not all of the HPβCD has been removed. The ability to completely remove the HPβCD from the bicomponent fiber provides corroborating evidence of a phase separated system. It should be noted that the visible peak at ~1670 cm\(^{-1}\) is from the -C=O stretching from the carbonyl group of DMF indicating a small amount of solvent remains in the as-spun fibers, however it is not visible in the regenerated fibers since it likely leached out during water treatment.

To confirm further that the HPβCD in the bicomponent fiber is indeed removed via water treatment the vacuum dried mats were weighed before and after regeneration of the porogen. Table 5.1 shows the weight loss percentages of the PAN and PAN/HPβCD bicomponent fibers after water treatment. A close match of the mass loss from the bicomponent fibers with the expected amount based on fiber loading verifies that HPβCD is easily removed during water treatment and is a further indication that phase separation is occurring during the evaporation of DMF during the electrospinning process.

The WAXD diffraction patterns for PAN, HPβCD and blends are presented in Figure 5.7. The semi-crystalline nature of PAN can be seen in a broad peak at \(\theta = 17.2^\circ\) due to the (100) plane of a hexagonal unit for both the PAN fibers and the regenerated blend suggesting
that HPβCD has been removed\textsuperscript{28}. The 50/50 as-spun fibers exhibit a more highly diffuse reflection pattern indicating that fibers become more amorphous and look similar to the amorphous diffraction pattern of HPβCD further corroborating the successful incorporation of HPβCD in the fibers.

The phase separation process in a binary mixture of components upon evaporation of a solvent can be quite complex. Not only is the solvent becoming incompatible with the components but also the components are becoming incompatible with each other simultaneously during evaporation. Additionally, since PAN is a semi-crystalline polymer, crystallization is also occurring which adds to the complexity. However, it is apparent that this system is phase separated and the complete removal of one component suggests that a bicontinuous, interconnected morphology exists, which is frequently seen in polymer mixtures undergoing spinodal decomposition (SD). Bognitzki \textit{et al}\textsuperscript{10} saw a similar behavior in studying the selective removal of PLA from PVP fibers during annealing. Additionally, Peng \textit{et al}\textsuperscript{34} conjectured that SD occurred in PEO/PAN fibers upon evaporation of DMF during the electrospinning process as well due to the abrupt changes in composition from the rapid evaporation of the solvent.

**5.3.3 Morphology of bicomponent fibers after HPβCD removal**

Fiber analysis from SEM images showed that the fiber diameters remained virtually unchanged after the removal of HPβCD (Fig. 5.5). The regenerated PAN and PAN/HPβCD bicomponent fibers are shown in Figure 5.8. The fibers remained continuous signifying that
microphase and not macrophase separation has occurred during the electrospinning process and that the HPβCD left voids within the fiber that did not collapse upon removal.

A more detailed look at the fiber morphology via high resolution SEM micrographs is shown in Figure 5.9. The PAN fibers (Fig. 5.9a and b) appear to be roughened and undulating at these magnifications. The surface morphology of as-spun PAN-HPβCD bicomponent fibers (Fig. 5.9c) are also rough in appearance with pitting and distortions. By examining the cross-section of the regenerated 50/50 blend (Fig. 5.9d), conspicuous nanoscale pore structures are evident. These pores structures appear to be interconnected and continuous throughout the fibers. By inspecting more closely the surface of these regenerated fibers, small pores are detected. Since these fibers must be sputtered with gold to prevent charging when performing high resolution SEM, we speculate that the pores on the surface are somewhat masked and/or partially covered by the metal coating, hence difficult to detect. The roughened morphology of all the fibers shown in Fig. 5.9 makes it difficult to discern the extent of the porosity present in the regenerated fibers.

In order to further probe the porosity of the fibers, nitrogen gas adsorption experiments were done in order to determine the specific surface area (SSA), pore volume and pore size distribution (PSD). The gas adsorption isotherms and PSDs for the as-spun fibers are presented in figure 5.10. The lack of hysteresis between the adsorption isotherms and desorption isotherms indicate that the fibers are not porous. In fact, no significant micro- (<2 nm) or mesopores (2-50 nm) are observed in the BJH (Barrett, Joyner, and Halenda) pore
size distribution (insets). Additionally, the volume of gas absorbed is directly proportional to
the fiber diameter of the sample (i.e. PAN fibers possess the smallest diameter and hence the
largest volume of gas adsorbed due to having the highest surface area). If we compare these
findings with the adsorption isotherms for the regenerated bicomponent fibers (Figure 5.11)
we see significant differences. The isotherms for the regenerated bicomponent fibers show
dramatically larger volumes of gas adsorption and substantially more hysteresis between the
adsorption and desorption isotherms. The shapes for the isotherms appear to be similar to
International Union of Pure and Applied Chemistry (IUPAC) classifications for Type II
adsorption isotherms with a hysteresis loop of the IUPAC H₃ classification often indicating
that the sample is made up of mesoporous platy aggregates or adsorbents containing slit-
shaped pores.⁴⁵

The pore size distributions (PSDs) were estimated using both BJH and NLDFT (Non-
local Density Functional Theory) methods (Figure 5.12, insets are for NLDFT). While many
methods have been developed to describe the adsorption-desorption capillary condensation
process that takes place in mesopores the BJH method is commonly used and is based on the
Kelvin equation:³⁵

\[
\ln \left( \frac{P}{P_0} \right) = -2\gamma v^l / r_k RT \quad (5.2)
\]

where \( \gamma \) and \( v^l \) are the surface tension and molar volume of the condensate, respectively, and
\( r_k \) (Kelvin radius), is the radius of the meniscus. The computation is usually based on the
notional removal of the condensate by a step-wise lowering of \((P/P_0)\) with allowance made at each desorption step for the thinning of the adsorbed multilayer in pores from which the capillary condensate has already been removed. The BJH method has the advantage of being a simple model but also a disadvantage in assuming that the Kelvin equation is applicable over the complete mesopore range. Nevertheless, it is still the most widely used method and is designed as ASTM standard method D4641/87 and is widely used also by commercial instruments to perform calculation on mesopores. Although the BJH method is not recommended for H₃ shaped isotherm loops due to the high “energy barrier” for condensation of materials in this classification, for the sake of comparison with other literature values, the BJH method was employed here. It should be noted that although the hysteresis shape most closely resembles that of an H₃ classification, no material can be perfectly described by one particular shape and tend to be a combination of classifications lending to the possible use of the BJH method to accurately describe the mesopores. The validity of choosing the BJH method will be further discussed later in the document.

The NLDFT method consists of the construction of a grand potential functional of the average local density and of a minimization of this with respect to local density to obtain equilibrium density profile and thermodynamic properties. A set of isotherms calculated for a set of pore sizes in a given range for a given adsorbate is called a kernel, and can be regarded as a theoretical reference for a given adsorption system. Such a kernel can be used to calculate pore size distributions from adsorption/desorption isotherms measured for the
corresponding systems. By employing the appropriate kernel, the NLDFT method allows for an accurate pore size analysis over the complete range of micropores and mesopores\textsuperscript{36}.

The PSD indicates that there are a significant number of pores in the mesoporous regime (2-50 nm) for all of the regenerated bicomponent ratios. Both methods of analyses, DFT and BJH, indicate that the fibers contain mostly mesopores and also some macropores (>50 nm). The BJH method, however, suggests that the material does not appear to have a significant amount of micropores present.

Surface area is an important parameter to consider for the characterization of porous solids. Despite the well-known limitations\textsuperscript{35} of the Brunauer-Emmett-Teller (BET)\textsuperscript{36} method, it continues to be widely used for the evaluation of the surface areas of microporous and mesoporous adsorbents. Usually two stages are involved in the evaluation of the BET area. First, it is necessary to transform a physisorption isotherm into the "BET plot" and from it to derive the value of the BET monolayer capacity, \( n_m \). The second stage is the calculation of the SSA, which requires knowledge of the molecular cross-sectional area of the adsorbate. The monolayer capacity, \( n_m \), is calculated from the adsorption isotherm using the BET equation, usually presented in its linear form\textsuperscript{35}:

\[
\frac{P/P_0}{n(1-P/P_0)} = \frac{1}{n_mC} + \frac{C-1}{n_mC} \left( \frac{P}{P_0} \right)
\]  

(5.1)
where the $P$ is the equilibrium pressure, $P_0$ is the saturation pressure, $n$ and $n_m$ are the adsorbed amount and the monolayer capacity, and a $C$ value that gives an indication of the attractive forces between the adsorbent-adsorbate interaction. In accordance with eq. 5.1 the BET plot of $[(P/n(P_0-P))]$ against $P/P_0$ should be a straight line with a slope of $[(C-1)/n_mC]$ and an intercept of $1/n_m$. The linear range for adsorbents of Type II isotherms is usually $[P/P_0 \sim 0.04-0.25]$ \(^{35}\). The SSA can then be determined from $n_m$ from Eq. 5.2:

$$SSA = n_mL\sigma$$ \hspace{1cm} (5.2)

where $L$ is Avogadro’s number and $\sigma$ (0.162 nm\(^2\) for N\(_2\)) is the average area occupied by each adsorbed molecule in the completed monolayer. The BET SSAs for both as-spun and regenerated bicomponent fibers are presented in Figure 5.13.

Porosity is confirmed by a large increase in the BET surface area when comparing as-spun with regenerated bicomponent fibers. There is an over 14-fold increase in the BET-SSA from \(\sim 5.2\) m\(^2\)/g to \(\sim 74.8\) m\(^2\)/g when comparing the 50/50 as-spun fiber to the corresponding regenerated fiber. The smallest increase upon regeneration of the porogen is seen in the 90/10 fibers where the BET SSA increased 2-fold from \(\sim 19.2\) to \(\sim 38.7\) m\(^2\)/g. Previous studies reported that pores were generated by the selective removal of PEO from PAN fibers and Zhang and coworkers saw a maximum of only 2.5 time increase in BET-SSA (46.8 m\(^2\)/g) comparing 50/50 PAN/PEO (w/w) as-spun to regenerated fibers\(^{37}\). Similarly, Gupta et al. saw a maximum of only a 6-fold increase in SSA from the removal of gallium trichloride from nylon-6 fibers\(^{23}\). The as-spun bicomponent fibers show a decrease in SSA
with fiber diameter that’s consistent with fibers that are non-porous with an increasing fiber diameter (see fig. 5.5). For the regenerated fibers there is a continuous increase in the surface area with HPβCD concentration but begins to plateau at the highest concentrations of HPβCD. This indicates that as the as-spun HPβCD concentration increases, the average pore size become larger. However, there is still an even larger increase in total pore volume when compared to pore size which results in a larger surface area. The plateau in SSA may suggest that a maximum pore volume to pore size ratio has been reached and that any increase in porogen content would not produce higher surface areas. Although the pores for all regenerated fibers are mostly mesoporous, the peak in the pore size distributions for the regenerated fibers shifts to a higher value. We believe this is a result of larger pores being formed from increased HPβCD aggregate sizes present in the as-spun bicomponent fibers before removal because of the increased HPβCD content. The pore volumes and average pore diameters are presented in Table 5.2.

As mentioned earlier, the average pore size for the regenerated fibers increases with HPβCD content to a maximum of 41.4 nm average pore width. The maximum in surface area corresponds with a maximum in pore volume to pore width ratio as seen for the 60/40 bicomponent fibers in Table 5.2. It is useful to compare both the BET surface area and Gurvich pore volumes to those derived from the BJH method. From Figure 5.13 there is a good agreement in trend between the SSA from both methods and from Table 5.2 the respective pore volumes match almost identically. This suggests that the BJH method may
indeed be an appropriate method in analyzing adsorption isotherms of the shape shown in Figure 5.11 for the regenerated bicomponent fibers. In view of the uncertainties and approximations made for both methods, however, one should not expect perfect agreement\textsuperscript{35}.

As with the SSA discussed previously, the values of pore volume observed for these fibers is much larger than those of other literature values previously reported for electrospun polymer nanofibers and twice as high as the largest found for PAN/PEO regenerated fibers (0.37 cm\textsuperscript{3}/g)\textsuperscript{18, 20, 23, 37}. It is anticipated that from the gas adsorption data presented, fibers could be tailored to a certain diameter and specific surface area depending on the requirement of the desired application. The surface area could be modulated by varying the ratio of PAN to HP\(\beta\)CD in the final fibers while the final fiber diameter may be adjusted by the overall concentration of the bicomponent in the electrospinning solutions.

5.3.4 DSC of Fibers

The DSC thermograms of a selected set of bicomponent (as-spun and regenerated) fibers along with the as-spun pure component fibers are shown in Figure 5.14. The DSC scan for pure PAN fibers shows a sharp exothermic peak at 299.7 °C from the thermal cyclization of PAN. The scan of HP\(\beta\)CD is flat with no peaks present showing that it is an amorphous solid as previously shown (Chapter 3). A summary of the thermal behavior of the samples of interest is shown in Table 5.3. The cyclization of PAN in the as-spun bicomponent fibers differs from the pure PAN and regenerated blend, represented as a shift in the cyclization temperature (\(T_{\text{cyc}}\)) and an increase in the heat of cyclization (\(\Delta H_{\text{cyc}}\)).
Furthermore, there was no significant change in the glass transition temperature ($T_g$) of the bicomponent fibers from the PAN nanofibers. It is well known that in compatible polymer blends there is usually a shift in the $T_g$ from the pure components to a $T_g$ that is between the $T_g$s of the two respective components\textsuperscript{38, 39}. Moreover, if the polymer and a non-polymer component have a substantial interaction, a detectable shift in the $T_g$ of the polymer can also be observed (As seen in PVA/HPβCD bicomponent fibers in Chapter 3). The lack of a shift in the $T_g$ of PAN indicates that the two species are not miscible confirming that PAN and HPβCD are indeed phase separated and not well mixed in the bicomponent fibers.

PAN is commonly used as a precursor for carbon fibers and undergoes a rapid exothermic cyclization reaction under heating. The reaction is highly dependent on both the physical and chemical states of the polymer along with the atmospheric and thermal conditions and other species that may be present during the reaction (i.e. remaining initiator residue, impurities, and end groups from polymerization). It has been well accepted that the pendant nitrile groups of PAN undergo a cyclization reaction during heating leading to ladder structures\textsuperscript{40, 41}. Although it remains difficult to confirm the ladder structure its existence has been inferred due to the high thermal stability, post-reaction color change and high modulus of the remaining thermally treated PAN product. Cyclization of pure PAN usually propagates through radical polymerization while PAN containing ionic impurities or copolymers progress through an ionic mechanism\textsuperscript{42}. The similar $T_{cyc}$ for the PAN fibers and regenerated PAN fibers indicate that the HPβCD has been removed. The altered cyclization
behavior of the PAN in the as-spun bicomponent fibers are a result of an abundance of hydroxyl groups present the HPβCD contained in the bicomponent fibers. The hydroxyl groups provide additional ionic groups that aid in both the initiation by lowering the activation energy (lower $T_{cyc}$) and the propagation of ionic mechanism (higher $\Delta H_{cyc}$) of the cyclization of PAN. Similar behavior was seen by Kim et al. with the addition of an ionic co-polymer to the polymer backbone containing PAN$^{42}$. Moreover, Zhang et al. attributed the difference in cyclization behavior in PAN/PEO blends to the presence of hydroxyl end groups on PEO chains$^{37}$.

5.3.5 Carbonization of Fibers

PAN is commonly used as a precursor to generate carbon materials by a controlled decomposition via stabilization and pyrolyzation steps. The stabilized PAN (from cyclization reaction) is thermally stable up to or above 800 °C. In a later step (carbonization/pyrolysis) all unstable components are pyrolyzed leaving only a carbon structure. The TGA thermograms that are representative of the weight loss of the electrospun PAN, HPβCD and bicomponent fibers undergoing the stabilization and pyrolyzation steps are shown in Figure 5.15a. The TGA conditions used were identical to those when the controlled decomposition is performed in a tube furnace to obtain large quantities of fibers for further analysis. The conditions are: stabilized at 280 °C for 5.5 under air and then carbonized at 800 °C for 1 hour under nitrogen. This set of conditions was chosen to allow us to compare our results with that of Ji et al$^{25}$. 

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All fibers showed an initial weight loss of water above at around 100 °C. An additional weight loss step was present for each of the fibers between 260 and 280 °C. For the as spun PAN fibers this is due to the elimination of the noncarbon elements in PAN which is approximately 22% of its initial weight. Furthermore, the weight loss between 260 and 280 °C increases with the increase in HPβCD content. The PAN/HPβCD bicomponent fibers have weight losses of approximately 54% and 62% for blends of 70/30 and 50/50 respectively owing to the degradation of HPβCD, which loses about 85% of its mass during the stabilization step for the pure component. However, it appears that after the stabilization step in air, the bicomponent fibers appear to be more thermally stable and the weight loss from the carbonization step was 18% and 15% for the 70/30 and 50/50 blends, respectively, while the additional weight loss in this step for the PAN fibers was approximately 35%. This thermal stability could be attributed to the reduction in activation energy associated with the cyclization reaction. The reduction in activation energy as earlier observed was evidenced by a drop in the $T_{\text{cyc}}$ and an increase in $\Delta H_{\text{cyc}}$ due to the presence of HPβCD, hence producing more thermally stable fibers.

From Figure 5.15b, it can be seen that the onset temperature for the decomposition of pure HPβCD in air is approximately 310 °C, which is higher than the stabilization temperature used for this study. As a result, HPβCD will be present during the stabilization of PAN such that the ladder structure created will form a rigid framework and lock the morphology of polymer around the HPβCD. Moreover, the removal of the HPβCD during
the carbonization process allows for the formation of a porous carbon fiber without the need for further processing. The remaining weight (8%) at 800 °C as seen in the thermogram for neat HPβCD represents the remaining char similar to what is seen from the decomposition of cellulosic materials²⁸.

SEM micrographs of carbonized bicomponent fibers that have undergone stabilization in air followed by carbonization in nitrogen are shown in Figure 5.16. The micrographs indicate that regenerated bicomponent fibers have a smoother morphology (Figures 5.16a and 5.16c), while the carbon fibers prepared from PAN/HPβCD as-spun bicomponent fibers appear more textured (5.16b and 5.16d). As the HPβCD content increases from 30% to 50% the undulating, roughened surface appears to be exacerbated and more apparent. This roughened structure could be a result of the degradation of HPβCD and evolution of gases arising from the non-carbon portions of PAN during the carbonization process. However, it is difficult to determine the porosity of these fibers from SEM alone.

To further probe the pore structure of the porous carbon nanofibers, N₂ adsorption experiments were conducted to measure BET SSA and PSD. However, we found that nitrogen adsorption was not sufficient for the characterization of the micropore structure of these carbon fibers as equilibrium was unattainable even after several days. CO₂ adsorption experiments were then carried out. Carbon dioxide is commonly used to probe ultra microporous materials, particularly microporous carbons³⁶. This is because CO₂ adsorption is done at higher temperatures (273 K) where CO₂ is still ca. 32 K below its critical
temperature. Also, since the saturation pressure is very high (26140 Torr) for CO$_2$, the relative pressure measurements necessary for the micropore analysis are achieved in the range of moderate absolute pressures. Hence, due to higher relative pressures and temperatures associated with CO$_2$ it has a distinct advantage as an adsorbate when compared to nitrogen at cryogenic temperatures, where diffusion problems may arise. The use of CO$_2$ as an adsorbate then allows for the completion of the adsorption isotherm in a significantly shorter time span due to higher diffusion rates and more rapid equilibrium when compared to nitrogen at 77 K. Additionally, the range of analysis can be extended to even smaller pore sizes that may be accessible to CO$_2$, but not to nitrogen molecules. Moreover, the experimental setup necessary for CO$_2$ adsorption is much simpler since the higher absolute pressures necessary do not require a turbomolecular pump or low-pressure transducers.

Therefore, CO$_2$ adsorption was employed because of its aforesaid attributes of increased diffusion and lowered equilibrium times. A summary of the results from the CO$_2$ adsorption studies is presented in Table 5.4. The validity of using the BET equation for microporous materials is discussed in detail elsewhere$^{36}$. In summary, though there are limitations for the use of the BET equation for characterizing microporous materials it is still used as the primary comparative method. For such materials, the caveat is that the BET equation gives more of a relative surface area (RSA) than specific surface area (SSA) for microporous surface area. As long as the C value is positive and a good linear fit of the adsorption data can be obtained using the BET equation, it is within reason to use it as a comparative “measuring stick” for microporous RSA.
The Horvath-Kawazoe (HK) method\(^{36}\) was used to evaluate the volume due to micropores \(V_{\text{mic}}\) and median micropore size. The HK method accounts for the enhancement of the adsorption potential as the pore size decreases allowing the calculation of the \(V_{\text{mic}}\) and PSD from adsorption isotherms. This approach reflects a fundamental statistical analysis of a fluid confined to a slit pore (e.g., applicable to carbon molecular sieves and active carbons, but not for zeolites). The HK methods have an advantage over the classical methods of micropore analysis (e.g., the Dubinin-Radushkevitch (82 thommes) method) in that they are specific with respect to pore shape (i.e. slit, spherical, or cylindrical) and adsorbate-adsorbent interaction potential.

The RSAs for neat PAN and bicomponent as-spun and regenerated carbonized fibers are given in Table 5.4. Unlike other studies, we found neat PAN to produce a microporous structure under these carbonization conditions\(^{25}\). Ji and workers found neat PAN fibers to have SSA of approximately 30 m\(^2\)/g. Our study reveals fibers made under similar conditions to have RSA of 10-fold higher (333.4 m\(^2\)/g). Results are rarely exactly reproducible between studies due to nuances involved with the experimental equipment and conditions along with human error. Nevertheless, we believe the microporosity present could be produced from the evolution of gasses released during the carbonization process of PAN.

The \(V_{\text{mic}}\) and median pore widths, derived from the HK method, indicate that there is significant amount of microporosity present in all of the carbonized fibers studied, with a median pore width in the ultramicropore range (< 0.7 nm). Interestingly, the regenerated
fibers have a similar RSA, pore volume, and median pore width to that of carbonized neat PAN fibers. This may be due in part to the collapse of the pore structure during the thermal stabilization processing of the fibers, rendering them nonporous before eventual pyrolysis in which they become similarly microporous to that of neat PAN carbon fibers. An evidence of such attribution is the significant change in the fiber diameters between the regenerated and as-spun bicomponent fibers shown in Table 5.4. The average diameter decreases by 28 % and 24 % for the as-spun and regenerated fibers for the 70/30 and 50/50 blends, respectively. This hints that the as-spun fibers maintain their porous morphologies due to the stabilization of the PAN which is rigid enough to preserve the morphology of the HPβCD’s presence before the pyrolysis step. Furthermore, the larger diameter is consistent with our findings of the larger surface area, median pore diameters and micropore volumes for the as-spun carbonized fibers contain a larger void volume.

For comparison, Ji et al.\textsuperscript{25} and Peng et al.\textsuperscript{34} achieved surface areas of 359 m\textsuperscript{2}/g and 321.1 m\textsuperscript{2}/g and micropore volumes of 0.134 cm\textsuperscript{3}/g and 0.14 cm\textsuperscript{3}/g for carbonized PAN/PLLA and PAN/Poly(AN-co-MMA) bicomponent fibers, respectively. The highest reported surface area (940 m\textsuperscript{2}/g) was attained by Kim and workers\textsuperscript{43} by the carbonization of PAN/PMMA bicomponent fibers. Although the values for surface area and pore volume presented here compare well to other literature in this area, it is important to remark that the analysis of the carbon fibers only probed the microporous domain and that to fully understand the structure of these fibers additional adsorption experiments would need to be explored. It is expected that there would be additional contributions to the surface area and
total pore volume from the meso- and macropore domains possibly present in these fibers. Additionally, analogous to the porous PAN polymer fibers presented earlier, a certain amount of tailoring in surface area and fiber diameter might be achievable by modulating not only the blend ratios and total solute contents in the electrospinning solutions but also the stabilization and carbonization steps as well.

5.3.5.1 WAXD and Raman Spectra of Carbon Fibers

To understand the carbon structure present in the carbonized PAN and bicomponent fibers WAXD patterns and Raman Spectra were studied. The XRD patterns (Figure 5.17a) show a large sharp peak at $2\theta = 25-26^\circ$ and a smaller broad peak near $2\theta = 44^\circ$ which correspond to the graphite layer structure (002) and (100)\(^4^4\). The average interlayer spacing $d_{002}$ and crystallite dimensions $L_{c(002)}$ were determined using the Bragg (eq. 5.4) and Scherrer (eq. 5.5) equations, respectively:

$$n\lambda = 2 \ d \ sin\Theta \quad (5.4)$$

$$L_c = \frac{0.91\lambda}{\beta} \ cos\Theta \quad (5.5)$$
where \( L_c \) is the apparent crystallite size along the c-direction, \( \theta \) is the scattering angle, \( n \) is an integer, \( d \) is the spacing in the atomic lattice, \( \lambda \) is the wavelength of the x-ray used and \( \beta \) is the half-maximum line width in radians.

Raman spectroscopy has been recognized as one of the most sensitive techniques for studying the structural properties of carbonaceous materials\(^{45}\). The Raman spectra for chosen carbon fiber samples are shown in Figure 5.17b. There were two broad overlapping peaks, one peak centered near 1590 cm\(^{-1}\) (G band) which is indicative of the high frequency E\(_{2g}\) first-order graphitic crystallites of the carbon and the other peak centered near 1350 cm\(^{-1}\) (D band) which is indicative of structure defects and disorder-induced features of the carbon. It is well known that the decrease in the ratio of the integrated intensity of D band (I\(_D\)) to G band (I\(_G\)), denoted by \( R = I_D/I_G^{45-47} \), suggests an increase in the graphite mole fraction where the graphite mole fraction \( x_G \) can be estimated by \( x_G = I_G/(I_D+I_G) \). Knight et al.\(^{47}\) have shown that the in-plane graphite crystal size \( L_a \) (a-direction) depends on \( R \):

\[
L_a = \frac{4.4}{R}
\]  

A summary of results describing the carbon structure from WAXD and Raman is presented in Table 5.5. From Table 5.5 it appears that the carbon structure is very similar for all of the bicomponent fibers, regardless of the presence of HP\(\beta\)CD during carbonization. This could be due to the change in the cyclization elucidated through DSC results (Fig 5.13 and Table 5.3) in which the exothermic reaction of cyclization changed for all bicomponent fibers.
Based on high $L_c$ and $L_a$, and compared to literature, it appears that these carbon fibers are significantly crystalline and all contain a graphite mole fraction of higher than 0.3.

**5.4 Conclusions**

Herein we have demonstrated bicomponent nanofibers of PAN and HPβCD are achievable through electrospinning. It has been confirmed that these components phase separate upon rapid evaporation of the solvent (DMF) during solvent casting and electrospinning and that HPβCD can be easily removed through water treatment. The removal of HPβCD was verified by FTIR, DSC, XRD, and weight loss experiments. Moreover, PAN was shown to be sufficiently rigid to maintain the voids created by the removal of HPβCD to generate highly-porous polymer nanofibers with high specific surface areas (up to $77.41 \text{ m}^2/\text{g}$) determined by nitrogen gas adsorption. To our knowledge, these are the highest specific surface area electrospun polymer nanofibers, PAN or other polymers, that has ever been achieved based on the open literature. The surface area of as-spun fibers, before water treatment, was found to be directly proportional to the fiber diameter. The diameters of the fibers ranged from an average of 223 nm (neat PAN) to 930 nm (50/50 PAN/HPβCD) and is inversely dependent with viscosity. The largest increase in SSA between as-spun and regenerated fibers was more than 14-fold, also the highest increase reported in the literature, to our knowledge.

PAN and bicomponent fibers were also used as precursors to the production of carbon fibers. It was found that by retaining the HPβCD in the fiber during the stabilization process,
then burning it off during the carbonization process, allows for voids to form within the fiber also maintaining a higher average fiber diameter as compared to the regenerated fibers. The carbonized, regenerated fibers were found to have a similar relative surface area to that of neat PAN fibers, indicating that they lost their porous morphologies during the stabilization process. This was further confirmed by an increase in microporous pore volume and mean pore width in the carbonized as-spun bicomponent fibers. The surface areas of the carbonized as-spun fibers were approximately 1.8 times that of the corresponding regenerated fibers.

The use of HPβCD as a porogen for both polymer and carbon fibers provides an exciting avenue for making porous morphologies. HPβCD is a versatile molecule that is small enough to be easily removed during solvent treatment, yet it is an amorphous solid unlike many small molecules (i.e. salts) that may form large crystalline domains. Additionally, based on this work, it is anticipated that one could tailor both the fiber diameter and porosity by judiciously adjusting both the overall component concentration and ratio of components.
5.5 References


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Figure 5.1: Scheme for different methods for producing porous fibers: A) soaking the as-spun PAN/HPβCD fibers; B) stabilizing and carbonizing the as-spun fibers and C) soaking as-spun fibers then stabilizing and pyrolyzing the fibers.

Figure 5.2: Micrographs of cast films: a) PAN after water treatment, b) 50/50 as-cast and c) 50/50 following water treatment.
Figure 5.3: Micrographs of as-spun fibers electrospun from a) PAN and blends of b) 90/10, c) 80/20, d) 70/30, e) 60/40 and f) 50/50 PAN/HPβCD.
Figure 5.4: Solution parameters: a) viscosity and b) surface tension and conductivity for PAN and PAN/HPβCD blends aimed at producing fibers with indicated HPβCD loading.

Figure 5.5: Fiber diameters for PAN and PAN/HPβCD blends both as-spun and after water treatment.
Figure 5.6: FTIR spectra for PAN, HPβCD, and bicomponent 50/50 PAN/HPβCD fibers before and after water treatment.
Figure 5.7: Wide-angle X-ray diffraction patterns of PAN, HPβCD and bicomponent fibers as-spun and regenerated.
Figure 5.8: Micrographs of regenerated fibers electrospun from a) PAN and blends of b) 90/10, c) 80/20, d) 70/30, e) 60/40 and f) 50/50 PAN/HPβCD.
Figure 5.9: High resolution micrographs of PAN nanofibers (a and b) and 50/50 PAN/HPβCD c) as-spun and d) regenerated bicomponent fibers, porous structure circled in yellow.
Figure 5.10: Adsorption (red)-Desorption (blue) isotherms and pore size distributions for as-spun fibers of a) PAN and bicomponent b) 90/10, c) 80/20, d) 70/30, e) 60/40, and f) 50/50 PAN/HPβCD.
Figure 5.11: Adsorption (red)-Desorption (blue) isotherms and pore size distributions for regenerated fibers for a) PAN and bicomponent b) 90/10, c) 80/20, d) 70/30, e) 60/40, and f) 50/50 PAN/HPβCD.
Figure 5.12: Pore size distribution for regenerated a) PAN and bicomponent b) 90/10, c) 80/20, d) 70/30, e) 60/40, and f) 50/50 PAN/HPβCD (NLDFT method inset).
Figure 5.13: BET (black squares) and BJH cumulative (blue circles) surface area for PAN and bicomponent fibers a) as-spun and b) regenerated.
Figure 5.14: DSC thermograms of electrospun PAN, regenerated PAN (from 50/50 as-spun fibers), HPβCD and bicomponent fibers.
Figure 5.15: TGA thermograms of electrospun a) PAN, HPβCD, and as-spun bicomponent fibers undergoing stabilization and carbonization and b) HPβCD in air.
Figure 5.16: SEM micrographs of carbonized a) regenerated 70/30, b) as-spun 70/30, c) regenerated 50/50 and d) 50/50 as-spun bicomponent fibers.
Figure 5.17: WAXD patterns and Raman spectra of electrospun carbonized fibers of a) 50/50 as-spun, b) 50/50 regenerated, and c) PAN.

Table 5.1: Weight loss percent change in the fiber mats that were dried before and after soaking in water to estimate the amount of material removed.

<table>
<thead>
<tr>
<th>Blend</th>
<th>HPβCD in Fiber (%)</th>
<th>Weight Loss (%)</th>
<th>HPβCD Removed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAN</td>
<td>0</td>
<td>1.3</td>
<td>--</td>
</tr>
<tr>
<td>90/10</td>
<td>10</td>
<td>9.4</td>
<td>94.0</td>
</tr>
<tr>
<td>80/20</td>
<td>20</td>
<td>19.5</td>
<td>98.0</td>
</tr>
<tr>
<td>70/30</td>
<td>30</td>
<td>28.7</td>
<td>95.7</td>
</tr>
<tr>
<td>60/40</td>
<td>40</td>
<td>38.9</td>
<td>94.8</td>
</tr>
<tr>
<td>50/50</td>
<td>50</td>
<td>47.8</td>
<td>93.6</td>
</tr>
</tbody>
</table>
Table 5.2: Summary of results from nitrogen gas adsorption for regenerated bicomponent fibers of PAN/HPβCD including pore volume and mean pore width.

<table>
<thead>
<tr>
<th>Blend</th>
<th>Pore Volume(^1) (cm(^3)/g)</th>
<th>Pore Volume(^2) (cm(^3)/g)</th>
<th>Mean Pore Width(^3) (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90/10</td>
<td>0.191</td>
<td>0.198</td>
<td>19.83</td>
</tr>
<tr>
<td>80/20</td>
<td>0.311</td>
<td>0.313</td>
<td>20.64</td>
</tr>
<tr>
<td>70/30</td>
<td>0.567</td>
<td>0.570</td>
<td>36.56</td>
</tr>
<tr>
<td>60/40</td>
<td>0.704</td>
<td>0.707</td>
<td>36.64</td>
</tr>
<tr>
<td>50/50</td>
<td>0.774</td>
<td>0.775</td>
<td>41.41</td>
</tr>
</tbody>
</table>

Table 5.3: Summary of the thermal characteristics for PAN, HPβCD and regenerated and as-spun bicomponent fibers.

<table>
<thead>
<tr>
<th></th>
<th>(T_g) (°C)</th>
<th>(T_{cyc}) (°C)</th>
<th>(\Delta H_{cyc}) (J/g PAN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>113.5</td>
<td>299.7</td>
<td>478.5</td>
</tr>
<tr>
<td>100 (regen)</td>
<td>112.1</td>
<td>299.3</td>
<td>425.3</td>
</tr>
<tr>
<td>70</td>
<td>112.6</td>
<td>281.7</td>
<td>590.2</td>
</tr>
<tr>
<td>50</td>
<td>114.0</td>
<td>280.5</td>
<td>603.8</td>
</tr>
<tr>
<td>0 (HPβCD)</td>
<td>225.2</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
Table 5.4: A summary of the fiber diameters and gas adsorption parameters of carbon nanofibers carbonized at 800 °C in a nitrogen atmosphere.

<table>
<thead>
<tr>
<th>Blend</th>
<th>Fiber Diameter (nm)</th>
<th>RSA$^1$ (m$^2$/g)$^1$</th>
<th>$V_{\text{micro}}^2$ (cm$^3$/g)</th>
<th>Median Pore Width$^3$ (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAN</td>
<td>180 ± 83</td>
<td>333.4</td>
<td>0.114</td>
<td>0.593</td>
</tr>
<tr>
<td>70/30 (regen)</td>
<td>176 ± 35</td>
<td>354.4</td>
<td>0.118</td>
<td>0.604</td>
</tr>
<tr>
<td>70/30 (as-spun)</td>
<td>233 ± 23</td>
<td>617.2</td>
<td>0.148</td>
<td>0.658</td>
</tr>
<tr>
<td>50/50 (regen)</td>
<td>594 ± 65</td>
<td>366.2</td>
<td>0.124</td>
<td>0.600</td>
</tr>
<tr>
<td>50/50 (as-spun)</td>
<td>762 ± 53</td>
<td>554.9</td>
<td>0.153</td>
<td>0.644</td>
</tr>
</tbody>
</table>

Table 5.5: Summary of results for structural properties, derived from WAXD and Raman spectroscopy, of carbon nanofibers made from neat PAN fibers and PAN/HPβCD bicomponent fibers as-spun and regenerated.

<table>
<thead>
<tr>
<th>Sample</th>
<th>$2\theta$ (°)</th>
<th>$d_{002}$ (nm)</th>
<th>$L_{c(002)}$ (nm)</th>
<th>$R_I$ ($I_P/I_G$)</th>
<th>$L_a$ (nm)</th>
<th>$x_G$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAN</td>
<td>25.57</td>
<td>0.348</td>
<td>8.15</td>
<td>1.56</td>
<td>2.82</td>
<td>0.391</td>
</tr>
<tr>
<td>50/50 (regen)</td>
<td>25.51</td>
<td>0.347</td>
<td>8.40</td>
<td>2.10</td>
<td>2.08</td>
<td>0.323</td>
</tr>
<tr>
<td>70/30 (as-spun)</td>
<td>25.63</td>
<td>0.349</td>
<td>8.08</td>
<td>2.11</td>
<td>2.09</td>
<td>0.321</td>
</tr>
<tr>
<td>50/50 (as-spun)</td>
<td>25.65</td>
<td>0.350</td>
<td>8.39</td>
<td>2.13</td>
<td>2.07</td>
<td>0.320</td>
</tr>
</tbody>
</table>
CHAPTER 6

High Throughput Melt Electrospinning of Polycaprolactone Fibers
High Throughput Melt Electrospinning of Polycaprolactone Fibers

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6.1 Introduction

Polymeric nanofibers present an exciting avenue for commercial development and novel usage because of their inherent attractive features (1-9). The desirable attributes of nanofibers, which include high surface to volume ratio, ability for surface functionalization, and superior mechanical properties make them viable candidates for many potential applications including membrane technology, reinforced materials, sensors, textiles, tissue engineering and drug delivery, to name a few1-9.

Solution electrostatic spinning (electrospinning) is a well-known process capable of producing submicron polymeric fibers with diameters on the order of nanometers (nm) through electrostatic forces1,10-13. The standard setup for an electrospinning device consists of a grounded collector, a syringe or extruder, and a high voltage power supply. In electrospinning, a polymer solution or melt in liquid form is loaded, extruded at a constant flow rate forming a droplet at the tip. When a potential is applied the meniscus of the charged droplet begins to stretch towards the collector hence forming a Taylor Cone14. As the voltage is increased, if there is enough molecular cohesion, the cone extends into a fine

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jet that is elongated at high strain rates towards the collector while the solvent is evaporated simultaneously. As the electrified jet is strained and the solvent evaporates, submicron polymeric fibers are deposited in a random pattern on the collector as a nonwoven mat. Despite the potential advantages of solution electrospinning, it is a process that is solvent intensive and inherently low throughput because of the constraints imposed by the polymer solution parameters. These drawbacks have prompted efforts to synthesize nanofibers by melt electrospinning\textsuperscript{15-23}.

Melt electrospinning does not require the use of a solvent. Larrondo and Manley were the first to report on electrospinning a polymer melt more than 2 decades ago\textsuperscript{17}. They were able to spin fibers of approximately 50 microns (\textmu m) in diameter using electrical field strengths of 3-8 kV/cm and collection distances of 1-3 cm. Lyons and coworkers explored the effects of molecular weight (MW) and polymer tacticity on melt electrospun fiber morphology. It was found that fiber diameters increased exponentially with increasing MW for isotactic polypropylene. An extruder provided the molten polymer in their experiments while most other melt electrospinning reports have used a heated syringe-like apparatus\textsuperscript{21}. Although Lyons et al. used an extruder the flow rate used in the electrospinning experiments was not divulged, instead extruder speed (in rpm) were reported and in some cases the flow rate was set at 0 rpm electrospinning from residual material on the front of the die. In this work we have determined that flow rate is an important parameter and the lack of knowledge makes it difficult to decipher the effect of other parameters. Recently Zhou and co-workers were able to melt electrospin polylactic acid (PLA) fibers, with the finest average diameter
yet achieved (ca 800 nm) using polymer melts via a temperature controlled spinning environment\textsuperscript{24}. They found that spinning at lower temperatures suppressed the jet whipping instability, while at higher temperatures the instability was exacerbated forcing the polymer jet to take a more tortuous path to the collector allowing more time for the fiber to stretch and elongate.

Out of the many publications in the electrospinning field, only a small fraction of these are on polymer melts. Melt electrospinning is in its infancy, yet it has the most potential for commercialization due to the increased fiber yield it affords; not to mention the preclusion of using solvents in the electrospinning process. However, there are challenges the process faces. Finding the polymer properties and processing parameters that are critical in producing fibers from electrospinning polymer melts that can generate fibers with the same quality and size as solution electrospinning delivers, is one of them.

During the last decade poly(\(\alpha\)-hydroxy acids), mainly lactide and glycolide homo and co-polymers, have received much interest among bio-degradable/compatible polymers because of their potential use in the medical and pharmaceutical industry. Poly(\(\varepsilon\)-caprolactone) (PCL), a semi-crystalline polyester, falls into this category, and is attracting increasing attention due to its controllable degradation rates and mechanical properties for applications such as long-term drug delivery\textsuperscript{25-27}, tissue repair and regeneration\textsuperscript{4,5,7,28-30}, and implants and prostheses\textsuperscript{31}. PCL is used as our starting material and was chosen based on its
low melting point for ease of processing and its environmentally benign properties, being a biocompatible and biodegradable polymer.

The novelty of our melt electrospinning apparatus is due in part to the multiple hole spinneret die, combined with the use of a table top extruder which allows for even higher throughput than the lab scale syringe setups commonly used\textsuperscript{17-24}. As seen in Table 1, past researchers in the melt electrospinning field employed a single hole spinneret or syringe. The multiple hole spinneret allow a much larger overall polymer flow rate to be distributed amongst the many orifices versus a single hole system successfully creating a high yield, commercially attractive setup for production of polymer nanofibers.

\textbf{6.2 Experimental Section}

Commercially available PCL (trade named CAPA\textsuperscript{®}) pellets were donated by Solvay Caprolactones (Chesire, UK) and were used as received. Gel Permeation Chromotography (GPC) was used to determine the molecular weights of each sample by comparison with polystyrene standards. GPC of PCL samples were performed on a Waters system 2695 equipped with UV set at 690 nm and refractive index detectors. The analyses were carried out at 40 °C using THF as an efluent at a flow rate of 0.3 mL min\textsuperscript{-1}. One hundred and twenty microliters of the sample dissolved in THF (2 mg mL\textsuperscript{-1}) was injected into HR3E, HR4 and HR4E (Waters) system of columns connected in series. The SEC system was calibrated with polystyrene standards in the molecular weight range of 25-100 kDal, Differential scanning calorimetry (DSC) was done using TA instruments\textsuperscript{®} Q200 model calorimeter in order to
determine both the melting point (56.5±0.5 °C) and the heat capacity in the range of interest (2±0.1 J/g*K). Rheological experiments were performed using a Rheometrics ARES rheometer using 25 mm parallel plates with a 2 mm sample thickness. Results from GPC analysis along with zero-shear viscosity of the materials used are tabulated below (Table 2). Viscosities were determined from dynamic rheology data at each temperature. It was found that the Cox-Merz rule applied well for the polymers at the conditions they were measured, hence all the viscosities listed are dynamic viscosities derived from the oscillatory tests.

The base component of the electrospinning setup (Figure 1) is a ¾ inch single-screw extruder (Wayne Machine and Die) with an extended 30:1 barrel. Along the length of the barrel, four band heaters were used to establish four individual temperature zones. During operation, the final zone was set to the desired temperature and the other zones were incrementally decreased by 10-15 °C for each zone.

The die dimensions are listed in Table 3. A DC high voltage power supply (Matsusada AU60P*0.5) was ground to the extruder and the live line was connected to an aluminum collection plate where the electrical field was applied. In conventional electrospinning the electrical potential is commonly applied to solution/melt, however, in our case the potential was applied to the collection plate. This change in polarity was used to protect the electrical components of the extruder. The polymer was extruded through the multiple holes in the spinneret die and electrospun to the collection plate.
The morphology and size of the resulting electrospun nonwoven fiber mats were evaluated using scanning electron microscopy (SEM, Hitachi S-3200N®) operating at an accelerating voltage of 5 kV. The electrospun samples were coated by a K-550X sputter coater with Au/Pd ∼100 Å thick to prevent charging. It should be noted that fibers that were more than 10 standard deviations larger in size were not included in the statistical analysis because we believe they are artifact fibers coming from the start-up and shutdown of the experimental run.

6.3 Result and Discussion

Initial experiments were performed using a 0.05 cm diameter single hole spinneret die. Figure 2 shows the micrograph of these representative fibers obtained using this die. Even though we were able to spin fibers, a large variability in the diameter distribution is observed with some fibers as large as 30 µm while others were in the submicron range. The presence of submicron fibers was a promising indication that further optimization of the operating parameters may yield uniform nanofibers. The large variability in fiber size may be attributed to our inability to accurately control the flow rate with the single hole because the pump was sized for significantly higher flow rates. The extruder used in this study was originally designed to operate from 1-100 rpms. However, even at 1 rpm, the volume of the polymer available to electrospin was too great. When the polymer drop at the tip of the spinneret is extended by the electrical field, the corresponding fiber reduction was not appreciable. In addition, with the large spinneret diameter, the initial fiber diameter before
solidification may be too high for the electric field to whip sufficiently. To decrease the fiber diameter, we had the option of either using a pump sized for lower flow rates or split the flow into multiple streams by using a multiple hole spinneret. We took the latter option and designed two new multi-hole spinneret dies with 16 and 24 holes to divide the lowest available throughput.

Henceforth, the electrospinning was done at a setting below 1 rpm. Since the extruder was designed to run at a much higher rpm rating, the reliability of the flowrate below the 1 rpm setting was poor. Below 1 rpm the flow rate was inconsistent and pulsing as the extruder struggled to apply enough torque at such a low rpm. Lyons work listed a similar problem citing extruder speeds of 0 rpm to obtain the best quality fibers.21

In view of this, we designed a multiple-hole spinneret die as we hypothesized that using the multiple hole dies greatly improved the flow rate issue. The multiple holes distribute the polymer flow across multiple holes in order to reduce the volume available to electrospin at each site. Also, the size of the holes in which the polymer exits the die is greatly reduced. Based on the law of conservation of mass, with the same mass throughput, a multi-hole spinneret would generate smaller fibers than a single hole spinneret. Figure 3 shows fibers obtained with the multiple spinneret die at the same conditions as used to make the fibers shown in Figure 2. These fibers are much smaller, with an average diameter of around 570 nm, and have much less variability in size than the fibers shown in Figure 2, (with a standard deviation around 100). It is also important to note that the larger fibers
still present in Figure 3 were artifacts of the flow rate being higher initially in order to induce the electrospinning process since the smaller fibers, produced after reaching steady-state, are laying on top of larger fibers.

In Table 4 we present the results of our investigation on the effect of changing the polymer melt temperature on fiber characteristics, using the multi-hole spinneret die. Fibers were electrospun at temperatures ranging from 70-190 °C at various collection distances (5-15 cm) and electrical field strengths (30-60 kV). One major polymer melt property that is temperature dependent is viscosity and has been deemed to be the most important parameter in melt electrospinning based on past studies\textsuperscript{15,17,21,23}. Hence, we found it important to compare fiber size and quality with respect to different viscosities in relation to the other electrospinning parameters. Zero-shear viscosities were measured and the results are shown for all 3 polymers with different MWs in Table 2. As expected the viscosity of PCL in all MW decreased with increasing temperature. However, in relation to electrospinning, our data suggest that viscosity is not as crucial as what others have observed. The fibers with the smallest average diameter and its corresponding standard deviation were obtained using a collection distance of 5 cm, an applied electrical field of 30 kV and a temperature of 80 °C. Table 4 shows a summary of PCL-29K fibers collected at the temperatures specified. However, the average diameter of fibers electrospun at 130 °C increased considerably and was larger than 2 µm. It can also be seen that at temperatures above 130 °C the fibers appear to be fusing. What this indicates is that at this temperature when the polymer deposits on the collection surface, it is still above its melting temperature ($T_m \approx 55$ °C) causing the fibers to
fuse together, forming the relatively large fibers seen at 130 °C and up. Whereas when electrospinning was done below 130 °C, the deposited fibers were cooled sufficiently (below the PCL melting point), thereby preventing fiber fusion. It is apparent then that there is interplay between the polymers rheological characteristics and heat transfer from the fiber as it is pulled from the spinneret to the collection plate.

For PCL-48K and PCL-29K fibers were achievable at all temperatures; however with PCL-84K, they were unattainable at temperatures below 160 °C where the zero-shear viscosity exceeds 3400 kPa.s. It seems that the polymer viscosity threshold for fiber formation in melt electrospinning of PCL must be around 4000-5000 Pa.s based on these results. Melt elasticity seems to be important as well since the best fibers were achieved at the 70 and 80 °C for PCL-29K. However, it was difficult to decouple the importance of elasticity from the viscous effects of the melt. Most importantly, fibers with an average diameter of less than 400 nm were achieved using PCL-29K and submicron fibers were obtained using all 3 molecular weights. The smallest fibers melt electrospun previously in literature were 800 nm using PLA\textsuperscript{24}. It should also be noted that the smallest fibers achieved in this work are comparable in size to PCL fibers obtained from solution electrospinning\textsuperscript{32-34}.

An interesting phenomenon that arose from comparing the morphology of the fibers obtained from PCL-29K and the higher molecular weight PCLs was the difference in fiber uniformity. Fibers collected from electrospun PCL-48K and PCL-84K are shown in Figures 4a and 4b, respectively.
The fibers shown in Figure 4 are both submicron, however not as small as fibers produced using PCL-29K (Table 4). This is due to the higher viscosity of the melt for higher molecular weight grades of PCL. Nevertheless, the viscosity of the PCL-84K at 190°C is still much higher than that of PCL-48K at 160°C, yet smaller fibers were produced with PCL-84K. This again proves that viscosity is not the only crucial property of the melt in determining fiber morphology. As for the fiber size variability, it can be seen that the fibers in Figures 4a and 4b are very uniform. This can be attributed, in part, to improved polymer flow rate control with the higher viscosity polymers.

We mentioned above that the flow rate was erratic and hard to measure. However Table 5 presents a summary of flow rates calculated from measured flow rates for PCL-29K and the estimates for other molecular weights studied by relating the melt flow indices. Typical flow rates used for solution electrospinning are in the range of 0.1-1 mL/h with concentrations of usually less than 15 wt%. This means that the usual production rates for solution electrospinning is atmost in the range of 0.0025 to 0.025 g/min. By comparison, all of the conditions studied here exceed this output providing potential for a higher throughput system using by electrospinning the melt.

6.4 Conclusions

A potentially high throughput method based on melt electrospinning to produce submicron diameter polycaprolactone fibers, with diameters as small as 320 nm, was
developed via a single screw extruder. It was shown that the use of a multiple spinneret die allows the production of smaller fibers with improved homogeneity.

The best conditions for electrospinning fibers at any temperature were found to be at an electrical field strength of 6 kV/cm and a collection distance of 5 cm. The importance of zero-shear viscosity was also investigated and it was established that although viscosity plays a role in determining fiber morphology, it may not be the only crucial property in melt electrospinning. A viscosity threshold of 4000-5000 Pa.s was determined by which, above that value, fibers could not be produced. Polymer flow rate was found to be a vital parameter evidenced by the improvement in fiber quality seen by both the use of the multiple spinneret die and during the use of higher molecular weight PCL.
6.5 References


(3) Dosunmu OO, Chase GG, Kataphinan W, Reneker DH. Electrospinning of polymer nanofibres from multiple jets on a porous tubular surface. Nanotechnology 2006;17(4):1123-1127.


(10) D. Li YX. Electrospinning of Nanofibers: Reinventing the Wheel? Advanced Materials 2004;16(14):1151-1170.


(14) Yarin AL, Koombhomce S, Reneker DH. Taylor cone and jetting from liquid droplets in electrospinning of nanofibers. Journal of Applied Physics 90(9):4836-4847.


Figure 6.1 Schematic of extrusion based melt electrospinning setup, the undulating lines at the extruders exit represent the multiple fibers produced during the electrospinning process.
Figure 6.2 Micrograph of fibers (PCL-29K) collected using the single spinneret die with a die temperature of 70°C, 30 kV applied voltage, and 5 cm collecting distance.

Figure 6.3 Micrograph of fibers (PCL-29K) collected using the multiple spinneret die using a die temperature of 70°C, 30 kV applied voltage, and 5 cm collecting distance.
Figure 6.4 (a and b) Micrographs of a) PCL-48K fibers (mean diameter 980 nm) collected using a die temperature of 160°C and b) PCL-84K fibers (mean diameter 770 nm) collected using a die temperature of 190°C, both using an applied voltage of 30 kV, and 5 cm collecting distance.

<table>
<thead>
<tr>
<th>Melt E-spinning</th>
<th>Spinneret type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larrondo (17-19)</td>
<td>2.2 mm (single) syringe</td>
</tr>
<tr>
<td>Lyons (20)</td>
<td>1.5 mm (single) extrusion</td>
</tr>
<tr>
<td>Dalton (15-16)</td>
<td>0.81 mm (single) syringe</td>
</tr>
<tr>
<td>Mitchell (22)</td>
<td>1 mm (single) syringe</td>
</tr>
<tr>
<td>Zhou (24)</td>
<td>0.84 mm-0.13 mm (single) syringe</td>
</tr>
</tbody>
</table>
Table 6.2 Molecular weights of the three grades of PCL and their respective zero-shear viscosities at each die temperature used for electrospinning.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PCL-29K</td>
<td>29120</td>
<td>763.5</td>
<td>541.6</td>
<td>275.4</td>
<td>129.7</td>
<td>69.7</td>
<td>35.7</td>
</tr>
<tr>
<td>PCL-48K</td>
<td>47880</td>
<td>4332.6</td>
<td>2650.6</td>
<td>1377.3</td>
<td>650.7</td>
<td>355.5</td>
<td>243.6</td>
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<tr>
<td>PCL-84K</td>
<td>83660</td>
<td>32769.3</td>
<td>27650.8</td>
<td>13953.1</td>
<td>6377.6</td>
<td>3427.1</td>
<td>1965.4</td>
</tr>
</tbody>
</table>

Table 6.3 Dimensions for extrusion dies used in this study, the multiplier in front of the hole size representing the number of holes on the face of the die.

<table>
<thead>
<tr>
<th>Dimensions</th>
<th>Single Spinneret Die</th>
<th>Multiple Spinneret Die</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length (in)</td>
<td>1.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Hole size (mm)</td>
<td>0.05</td>
<td>24 x 0.015</td>
</tr>
</tbody>
</table>
Table 6.4 PCL-29K fibers electrospun at a 5 cm collecting distance using a 30 kV electrical field at various temperatures listed.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Viscosity (Pa.s)</th>
<th>Fiber Statistics (nm)</th>
<th>Fiber Statistics (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>763.5</td>
<td>AVG: 573.9 SD: 101.5 MIN: 336.7</td>
<td>AVG: 323.7 SD: 58.5 MIN: 259.6</td>
</tr>
<tr>
<td>80</td>
<td>541.6</td>
<td>AVG: 323.7 SD: 58.5 MIN: 259.6</td>
<td>AVG: 323.7 SD: 58.5 MIN: 259.6</td>
</tr>
<tr>
<td>100</td>
<td>275.4</td>
<td>AVG: 399.7 SD: 58.5 MIN: 325</td>
<td>AVG: 2328.6 SD: 936.7 MIN: 767.3</td>
</tr>
<tr>
<td>130</td>
<td>129.7</td>
<td>AVG: 399.7 SD: 58.5 MIN: 325</td>
<td>AVG: 2328.6 SD: 936.7 MIN: 767.3</td>
</tr>
<tr>
<td>160</td>
<td>69.7</td>
<td>AVG: 9511.8 SD: 4942.1 MIN: 1221.7</td>
<td>AVG: 4573.9 SD: 1673.5 MIN: 433.5</td>
</tr>
<tr>
<td>190</td>
<td>35.7</td>
<td>AVG: 9511.8 SD: 4942.1 MIN: 1221.7</td>
<td>AVG: 4573.9 SD: 1673.5 MIN: 433.5</td>
</tr>
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</table>
Table 6.5 Summary of polymer flow rates calculated using a known flow rate and relating them through MFI and viscosity.

<table>
<thead>
<tr>
<th>Polymer</th>
<th>MFI (160°C)</th>
<th>70 ºC (g/min)</th>
<th>80 ºC (g/min)</th>
<th>100 ºC (g/min)</th>
<th>130 ºC (g/min)</th>
<th>160 ºC (g/min)</th>
<th>190 ºC (g/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCL-29K</td>
<td>48.0</td>
<td>0.046</td>
<td>0.064</td>
<td>0.127</td>
<td>0.269</td>
<td>0.500</td>
<td>0.976</td>
</tr>
<tr>
<td>PCL-48K</td>
<td>9.0</td>
<td>0.008</td>
<td>0.013</td>
<td>0.026</td>
<td>0.055</td>
<td>0.100</td>
<td>0.146</td>
</tr>
<tr>
<td>PCL-84K</td>
<td>3.0</td>
<td>0.003</td>
<td>0.004</td>
<td>0.007</td>
<td>0.016</td>
<td>0.030</td>
<td>0.052</td>
</tr>
</tbody>
</table>
CHAPTER 7

Conclusions and Recommendations


7.1 Conclusions

In the preceding chapters, we explored the incorporation of cyclodextrins into submicron fibers via electrospinning. We discovered that it is possible to electrospin fibers from cyclodextrin alone in several solvents, expanding the current perspective of what is considered “electrospinnable”. In another embodiment we combined CDs with other electrospinnable polymers to investigate its effects on solution and fiber properties. In one case, CDs were mixed with a compatible polymer that did not phase separate during electrospinning and was crosslinked to form water resistant materials. In another case we exploited the complexation ability and extreme solubility of CDs to create fast dissolving, drug loaded membranes. We combined CDs with a system that phase separated during electrospinning to produce domains which could be leached out or pyrolized to form a porous nanofiber structure. And finally, a novel, extrusion based melt electrospinning setup was designed and studied for potential in creating a method for high throughput electrospinning. Some of our specific and additional major findings are summarized below:

- We illustrated that modified CDs (HPβCD and MβCD) can be electrospun into submicron fibers without the need for a “carrier” polymer. Typically, an electrospinnable polymer is necessary in order to produce fibers as a spinning aid with small molecules. The molecular cohesion necessary to prevent electrospaying usually provided by polymer chain entanglements is instead replaced by strong hydrogen bonding between CDs in solution. We found that it was necessary to have
very high concentrations of CDs (>60 wt%) to produce strong enough interactions to prevent capillary breakup during the electrospinning process. We also determined that the CDs could be electrospun using an array of different solvent systems, lending to its versatility. These findings provide a better understanding of what is necessary to electrospin and what might be electrospinnable. Additionally, the ability to produce functional fibers made of CDs could have many interesting applications.

- We examined the utility of electrospinning CDs by way of adding a compatible “carrier” polymer (PVA). The window for electrospinning CDs by themselves is limited and possible only at high concentrations. The effects of the addition of PVA to the spinning solutions were studied and the impact on electrospinnability was discussed. By adding PVA, the window for electrospinning bicomponent fibers containing various amounts of CDs was expanded with some control over the fiber diameters and bicomponent ratios. Moreover, we found that PVA and CD formed a compatible dispersed fiber without signs of phase separation. Moreover, the -OH functionalities of the PVA and CD allow for crosslinking of the fibers to render them water resistant. These findings suggest that electrospun bicomponent fibers can be fabricated with control of its morphology, composition and dimensions using the CD-PVA compatible system and this could be extended further into other polymeric bicomponent systems.

- We investigated the use of this bicomponent compatible system for use in rapid dissolving membranes with the end in view of exploiting them in drug delivery. The
same property that makes chemically modified CDs so attractive, namely extraordinary solubilities, can be exploited in combination with the very high surface area associated with submicron fibers to produce rapid dissolving non-woven membranes. Fiber mats comprised of only CD dissolved completely in a matter of milliseconds while fibers containing increasing amounts of PVA required longer times to disintegrate. We found that the solubility of the drug in the spinning solutions to be directly proportional to the amount of cyclodextrin available for complexation. In addition, we established that the drug was amorphously distributed in the fibers. A drug in its amorphous state is much easier to dissolve and release than when it is in its crystalline form.

- We successfully incorporated CDs into a microphase separated domains within an incompatible polymer, PAN. Ocular inspection of the electrospinning solutions of the bicomponent system dissolved in DMF revealed a clear, stable solution with no visible signs of phase separation. However, upon electrospinning the system phase separated to produce bicomponent fibers consisting of PAN (continuous phase) with microphase separated domains of CD. Phase separation was confirmed by the presence of two distinct glass transition temperatures and the ability to completely remove the CDs from the bicomponent fibers. Leaching out of the CD produced a mesoporous PAN fiber with high specific surface area exceeding 70 m²/g. Furthermore, PAN fibers were converted into carbon fibers via stabilization followed by carbonization. It was found that carbonizing the bicomponent PAN/CD fibers
removed the CDs by pyrolysis creating microporous and mesoporous carbon structures. These findings suggest that CDs may be used as a porogen for systems for which stable electrospinning solutions can be achieved while phase separation occurs during the spinning process. Moreover, these fibers provide even higher surface areas than that of solid submicron fibers and could find use in templating, filtration, battery applications, and catalysis.

- We demonstrated the use of an extrusion based melt electrospinning device to produce submicron PCL fibers. Traditionally, electrospinning involves low concentration solutions dissolved in potentially harmful organic solvents. Electrospinning the melt allows for the production of fibers without the need for solvents and would be of particular interest as a biomaterial where the fiber mat has to be inevitably in contact with human tissues. Furthermore, polymers with limited solubility, such as polypropylene, could be electrospun. Additionally, by using an extrusion based system, the scalability of the process would be improved over a conventional needle-based setup.

7.2 Recommendations

In this dissertation research, we examined the major effects of incorporating CDs into various electrospinning systems. Also, we examined a device to aid in the development of a scalable, commercially viable electrospinning process. The scope of this research can be
extended to other systems. Some of our recommendations for future research are discussed below:

7.2.1 Electroblowing

Electroblowing is a hybrid technique used for creating submicron fibers by utilizing electrostatic spinning combined with a hot air stream that further attenuates the fiber jet. The hot air stream can aid in further stretching of the polymer jet and controlling the instabilities that arise during the electrospinning process (i.e. whipping instability). Currently, this technology is used to either improve the spinning of conventional electrospinning solutions (i.e. low concentration) or in spinning a polymer melt. However, electroblowing may find its best application in a system that contains high concentrations of spinning materials. This type of system would be too viscous to electrospin by traditional means and/or may not be melt-processable.

In Chapter 2 we discussed the ability to electrospin cyclodextrin molecules by themselves. However, we found that there was only a small window, controlled by high concentrations, at which cyclodextrins are electrospinnable. High concentrations resulted in very viscous solutions and therefore limited the fibers produced to being rather large (just less than 1 micron on average for HPβCD). Electroblowing could possibly extend this window by allowing for additional degrees of freedom, such as air jet velocity and jet temperature, effectively widening the range of fiber diameters achievable. In general, electroblowing of highly viscous solutions may provide a good compromise for many
systems and provide commercially viable material outputs. Furthermore, electroblowing might also be a useful extension of the work done in Chapter 6 to help overcome the high viscosities associated with polymer melts.

### 7.2.2 Core-shell Fibers

Core-shell (or coaxial) fibers consist of a core material sheathed by a layer of the same or a different material. This technique has been used to produce fibers with unique morphologies such as hollow tubes\(^6\). Additionally, coaxial electrospinning provides an opportunity to electrospin materials, as a part of the core or sheath, that are not able to be spun by themselves. A particularly interesting application of nanofibers with a core-shell geometry is in tissue scaffolding, where they perform a dual role in providing mechanical support while also serving in the delivery of bioactive agents\(^7\). To our knowledge, CDs have not yet been introduced into these types of fiber geometries. CDs could serve as a means to elute drugs or other agents from either the core or the sheath. As a sheath material they could be used to rapidly deliver anti-inflammatory drugs directly to the implantation site to aid in healing. When used as a core material the drug release could be controlled by the diffusion properties of the sheath or by its bioerosion rate. Since we found that CDs can be well dispersed (Chapter 3 and 4) or phase-separated (Chapter 5) within a polymer matrix an opportunity for controlling the release from a bicomponent or tricomponent core-sheath fibers may be possible by judiciously selecting the system’s components.
7.2.3 Extensions of Current Work

- In Chapter 2, we demonstrated that cyclodextrins (M\(\beta\)CD and HP\(\beta\)CD) could be electrospun, by themselves, to create submicron fibers. This extends the perspective by which electrospinnability is viewed. Naturally, other chemically modified CDs could be explored (hydroxyalkylated, acetylated, sulfonated, and \(\alpha\)- and \(\gamma\)- versions as well). McKee et al\(^8\) demonstrated that a phospholipid, lecithin, could be electrospun through self-assembly that emulates polymer entanglements. The more interesting implications of this work would be to find other types of small molecules that will spin. For example, other amphiphiles, such as ionic surfactants that form wormlike micelles in an aqueous medium.

- In Chapter 3, we showed the ability to electrospin bicomponent fibers of PVA and HP\(\beta\)CD. We found that the pseudo-entanglement concentrations were lowered upon the addition of CDs to PVA in solution. Our proposition is that CDs could be used in a similar role with other polymers as an electrospinning aid. For instance, alginate is not electrospinnable without the addition of surfactants and other electrospinnable polymers (PEO or PVA) (recently submitted work to Biomacromolecules, Saquing et al). This lack of spinnability is attributed to a combination of: lack of adequate entanglements, high conductivity, and high surface tension. We found that HP\(\beta\)CD
effectively increased entanglements and lowered conductivity when added to PVA. It may be possible for CDs to serve a similar purpose for alginate or similar polymer systems while maintaining biocompatibility. This would mean that the CDs will be acting in a reverse role and as an electrospinning aid itself.

- In addition, in Chapter 3 we examined the ability to crosslink PVA/HPβCD fibers ex-situ by soaking in EGDE at an elevated temperature. This type of post treatment may not be suitable for larger scale production of crosslinked fibers with the additional problem of removing residual crosslinker in the post treatment. Therefore, we recommend the use of a crosslinker in-situ, during electrospinning, to produce water resistant polymer fibers in a one-step process. Tang et al already studied reactive electrospinning of PVA with glutaraldehyde as the crosslinker. Similarly, CD or CD containing bicomponent fibers with PVA could be reactively crosslinked to create functional water resistant fibers that could be interesting filter materials or controlled drug release membranes.

- CDs were studied as a porogen for both PAN and carbon fibers in Chapter 5. A natural extension of this work would be to explore CDs as a porogen for other polymers, such as nylons, polymethacrylates, polyesters, etc. As mentioned earlier, the use of CDs as a porogen provides an amorphous, small
molecule that is easily removed while allowing for different degrees of porosity depending on blend ratios. It would also be of interest to study these porous polymer fibers as filtration or templating materials. Furthermore, it has been shown that mesoporous materials aid in cell proliferation and could find applications in tissue scaffolding.
7.3 References


