Electrospun PLA : PCL/ halloysite nanotube nanocomposites fibers for drug delivery

H. Haroosh

Department of Chemical Engineering, Curtin University of Technology, Perth, Australia

D. Chaudhary (*)

Department of Chemical Engineering, Curtin University of Technology, Perth, Australia

Y. Dong

Department of Mechanical Engineering, Curtin University of Technology, Perth, Australia

B. Hawkins

Department of Chemical Engineering, Curtin University of Technology, Perth, Australia

Abstract

This research work focused on PLA and blends of PLA with poly (ε-caprolactone) and that are reinforced with two different concentration of halloysite nanotubes (HNT) and different kind of co-solvent for electrospinning (chloroform: acetone), (chloroform: methanol) and (dichloromethane: N,N, dimethylformamide). Fiber properties were found to be related to the viscosity and conductivity of the bulk solution. Initial results showed that the fiber surface morphology is strongly dependent on the solution mixture and HNT amounts. The uniform bi-component PLA–PCL fibers were obtained and also the fiber diameter was found to be dependent on the content of PLA–PCL, type of co-solvents and HNT amount. Solution viscosity, conductivity and solvent volatility were the key factor that controlled the fiber diameter in the electrospinning. Further results evidently presented that raising the PCL amount in blends reduces the solution viscosity and higher viscosity led to fibers with larger diameters. Scanning electron microscopy (SEM) and DSC have been used to characterise these bionanocomposites and a simple process relationship was proposed to offer better understanding on the structure-property relationship of these advanced materials.

*Corresponding author's E-mail address: d.chaudhary@curtin.edu.au

Introduction

Electrospinning is a multipurpose polymer processing technique in which a stream of a melt or polymer solution is connected to a high electric field, resulting in formation of nanodimension fibers. It offer a promising way to fabricate continuous fibers with diameter ranging from nanometers to microns (Han et al. 2009). The electrospun nonwoven fabrics consisting of ultrafine fibers find wide applications as separation filters, carbonaceous materials (Han et al. 2009) and biomedical devices including scaffolds for tissue engineering, tissue repair substitutes, wound dressing materials, and carriers for drug delivery platforms, due to their high specific surface area and porous structure (Cui et al. 2006).

Biodegradable polymers offer sustained release of encapsulated drugs, low-molecular weight materials, and degradability. Polymers have been commonly used in several applications in the pharmaceutical industry as carrier for tissue engineering and drug delivery. The electrospun polymer nanofibrous materials can be used as carriers for hydrophobic and hydrophilic drugs. The modulation of the scaffold's morphology, porosity and composition, allows control of the drug release profile. The most important advantage of this method is that it offers site-specific delivery of drugs from the scaffold into the body(Kim et al. 2004). Up to now, electrospinning has been used for the fabrication a numerous biodegradable polymers for drug delivery, such as poly- (lactic acid) (PLA), poly(ε-caprolactone) (PCL), poly(glycolic acid) (PGA), poly(lactide-co-glycolide) (PLGA) and polyurethane (PU); natural proteins have been used including collagen, gelatin and elastin (Heydarkhan-Hagvall et al. 2008). In addition, for successful electrospinning, it is essential to choose an appropriate solvent system that should be able to dissolve the polymers (Buschle-Diller et al. 2007; Han, Branford-White, and Zhu 2010).

High molecular weight poly(lactide) (PLA) provides mechanical strength and integrity to the scaffold (Kim et al. 2004) and so are promising for clinical uses, because the acidic environment induced by the degradation of the polymer helps to reduce bacteria growth and promote epithelization. This is mainly due to their biocompatibility and the flexibility they offer in terms of their degradation profiles, and mechanical properties (Cui et al. 2006). Also, Poly(ε-caprolactone) (PCL) is well known for its slow biodegradability, high biocompatibility, and good drug permeability (Luong-Van et al. 2006; Kenawy et al. 2009). Halloysite nanotubes (HNT) are clays belonging to the kaolinite group. HNT is tubular with length in the

range of 1 to 3 mm and diameter in the range of 100 to 300 nm. They are formed by rolling octahedral sheets of alumina and the layers of tetrahedral sheets of silica. It has been recently reported that because of the hydroxides groups in the HNT structure, the incorporation of HNT within PLA polymer can resist the negative effect of PLA acidic environment (Touny et al. 2010). This study investigates the effect of solvent and addition of HNT nanoclays on the electrospun fiber diameters of biopolymer blend of PLA and PCL.

Materials and methods

Materials

Poly (ε-caprolactone) PCL (Mn = 33,000 g/mol) was purchased from Daicel Chemical Industries ltd Japan, poly lactide acid (PLA) 3051D, with a molecular weight (Mn) of 1.42 × 104 g/mol and a melting temperature of 170 °C was supplied by Nature Works USA (Fortunati et al. 2010), halloysite nanotubes (HNT) from Southern clay products USA , while Dichloromethane (DCM), dimethylformamide (DMF), chloroform and methanol were purchased from Sigma-Aldrich Ltd and these chemicals were used without any purification.

Electrospinning

Electrospinning was carried out using 8% w/v solution of PLA mixed with 15% w/v PCL at different ratio of 1:0, 3:1 and 1:1 in three solvents, namely DCM:DMF at 3:1, chloroform:methanol at 2:1 and chloroform:acetone at 2:1. The HNT was added at 1 % w/v and 2% w/v to all solvents and homogenized for 30 minutes using ultrasonication. For electrospinning, the solutions were transferred to a 10-ml syringe pump with needle specification of 20G. The flow rate of the polymer solution was 2 ml/h, and the applied positive voltage was in the range of 25-28 kV. The resulting fibers were collected on a flat aluminum foil. The distance between the needle tip and the target was 13cm. The thickness of nanofibers ranged from 300 to 450 μm.

Viscosity of solutions

The viscosity of solution was measured by using Visco 88 - a portable viscometer from Malvern instruments (UK), with built in temperature sensor, and supplied with a double gap measuring geometry to provide extra sensitivity when measuring low viscosity fluids.

Scanning electron microscopic (SEM) studies

The morphology of electrospun nanofibers was studied by an EVO 40XVP scanning electron microscope (Germany) and the accelerating voltage was set at 5 kV. Before SEM observation, the samples were sputter-coated with platinum. Fiber diameter was calculated from the SEM images by using an in-house developed scanning program, which analyses minimum of 50 fibers from a scanned SEM image, and includes a statistical deviation of 15%.

Differential scanning calorimetry (DSC)

DSC was performed using a DSC6000 Perkin Elmer with Cryofill liquid nitrogen cooling system. Approximately 10ug of fiber was sealed in aluminum pans and their thermal behavior was analysed during heating and cooling between 30^{o}C and 180^{o}C with a ramp rate of10^{o}C/min.

Results and discussion

Without HNT loading

Fig1 a. shows that using PLA in DCM: DMF led to homogenous fibers with average diameter of 450 nm with a large variation in fiber diameters. Increasing the amount of PCL to PLA (1:3) led to fibers with average diameter of 490 nm with maximum and minimum diameters 800 nm and 230 nm, respectively. Moreover, increasing the percentage of PCL (1:1) caused beads and inhomogeneity in structure with a decrease in diameter to 250 nm with maximum and minimum diameters 425nm and 130 nm respectively as shown in the Fig1c. This indicates that by lowering the solution viscosity, the fiber diameter can be reduced, but greater inhomogeneity occurs in the fiber structure and that is a possible reason for the beads to occur in the electrospinning process.

Moreover, Fig2 gives the result of viscosity of different percentage of PLA: PCL solutions dissolved in the mixture of DCM: DMF, chloroform: methanol and chloroform: acetone and it can be seen that increasing PCL led to decrease the viscosities of solution. Fig3a. showed that using PLA dissolved in chloroform: methanol produced good fibers with average diameter 510 nm and the maximum diameter was 740 nm. Raising the percentage of PCL to PLA (1:3) produced fibers with beads with average diameter 325nm with maximum and minimum diameters 390nm and 260 nm respectively and by increasing the percentage of PCL to (1:1) there was no fiber structure obtained. Considering that the solution viscosity is critical in forming fibers, Fig2 shows that the viscosity was significantly reduced by

addition of PCL in 1:1 ratio and its effect on the electrospun fibers was the same as seen with DCM: DMF solvent.The fibers produced from the DCM:DMF system for all percentages was more uniform resulting in smaller fibers as compared to fibers from chloroform: methanol system and this is because the conductivity of DCM:DMF solution is higher than the chloroform: methanol solution. Fig3 shows the SEM images of fibers produced using the chloroform: methanol solution. DMF has a higher dielectric constant than methanol while DCM has higher dielectric constant than chloroform. So, Increasing the conductivity aided in the production of uniform charge density and beads-free fibers and also higher conductivities yielded smaller fibers as shown earlier (Pham, Sharma, and Mikos 2006).

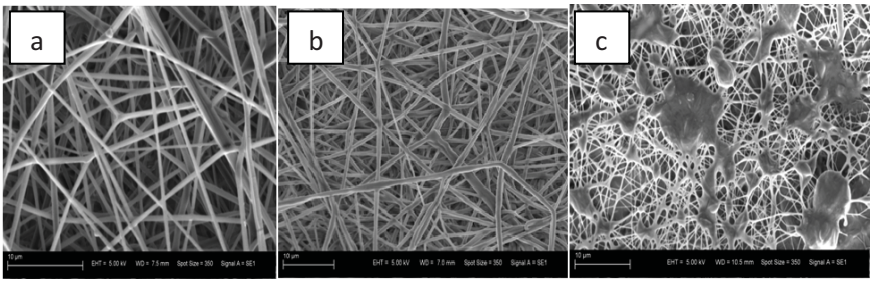

Fig1. SEM micrographs of electrospun PLA :PCL fibers by using DCM:DMF as a solvent and containing various PLA:PCL blend ratios (a) 1:0 wt%, (b) 3:1 wt%, and (c) 1:1 wt%.

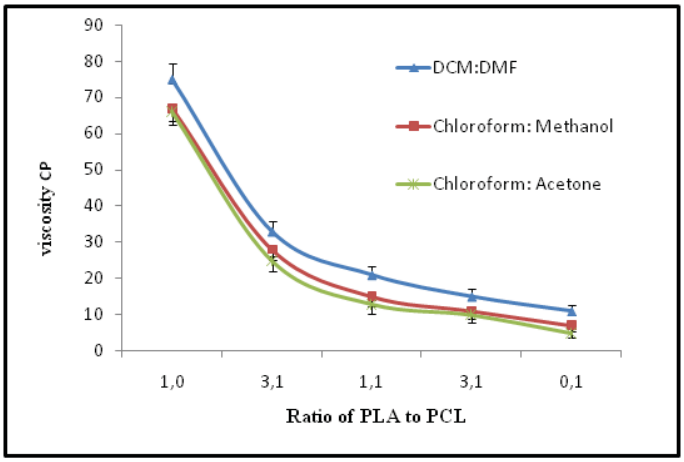

Fig2. Viscosity of different percentage of PLA: PCL solutions dissolved in the mixture of DCM: DMF, chloroform: methanol and chloroform: acetone.

Fig4 a. demonstrated that electrospun PLA dissolving in chloroform: acetone led to produce fibers with average diameter 570 nm with the maximum diameter was 775 nm, while increasing the amount of PCL to PLA (1:3) produced fibers with inhomogeneity in structure and the average diameter reduced to 375nm with

maximum diameter of 600 nm. Further increase in PCL led to no fiber formation as shown in Fig4 c. Table 1 shows dielectric constant for all solvents while Table 2 summaries the average fiber diameters for all structures. The significance of the solutions conductivity can be gauged from Table 1 and Table 2. For all polymer blends systems, fibers diameters and structural homogeneity showed strong correlation with the type of solvent used.

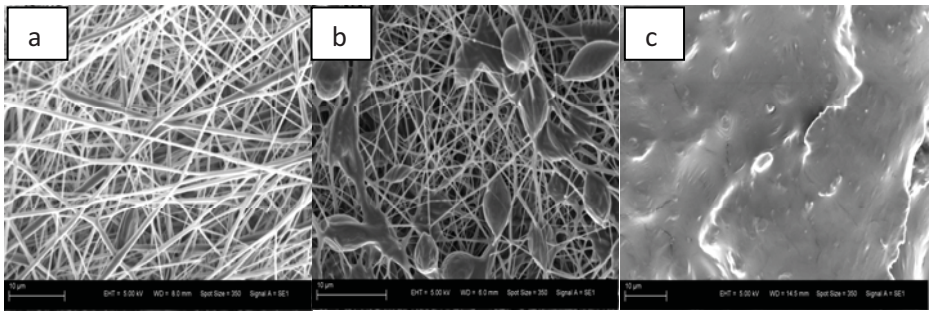

Fig3. SEM micrographs of electrospun PLA :PCL fibers by using chloroform:methanol as a solvent and containing various PLA:PCL blend ratios (a) 1:0 wt%, (b) 3:1 wt%, and (c) 1:1 wt%.

Table 1. Dielectric constant for solvents.

	DMF	Methanol	Acetone	DCM	Chloroform
Dielectric constant	38.3	33	21	9.1	4.8

Table 2. Summaries the all average fiber diameter for all structures.

	PLA:PCL (1:0)	PLA:PCL (3:1)	PLA:PCL (1:1)
DMF: DCM	450nm	490nm	250nm
chloroform: methanol	510nm	325nm	No fiber
chloroform: acetone	570nm	375nm	No fiber

Effect of HNT loading

With the addition of nanoclays, viscosities of the solutions tend to increase, even though the overall trend was decreasing as the PCL content was increased, as shown in Fig5 and this is similar to results reported elsewhere (Bhardwaj and Kundu 2010). Fig6, 7 and 8 shows that using PLA and blend PLA:PCL at different percentages have significantly dissimilar behavior. First, addition of nanoclay always increased the fiber diameters. This is because the viscosity of the solution

increased by the addition of inorganic clay and Table 3 shows the average fiber diameters for 1% and 2% HNT.

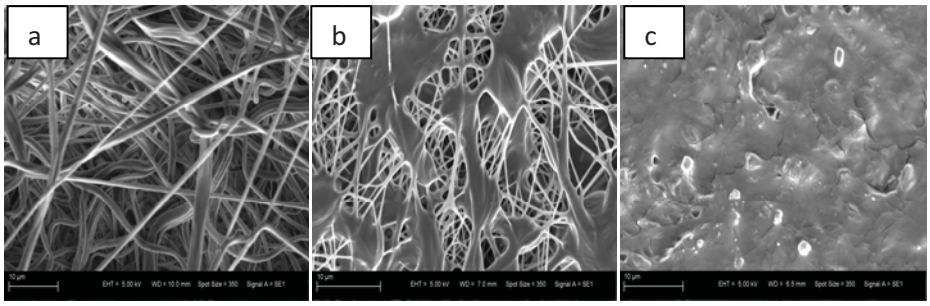

Fig4. SEM micrographs of electrospun PLA: PCL fibers by using chloroform: acetone as a solvent and containing various PLA: PCL blend ratios (a) 1:0 wt%, (b) 3:1 wt%, and (c) 1:1 wt%.

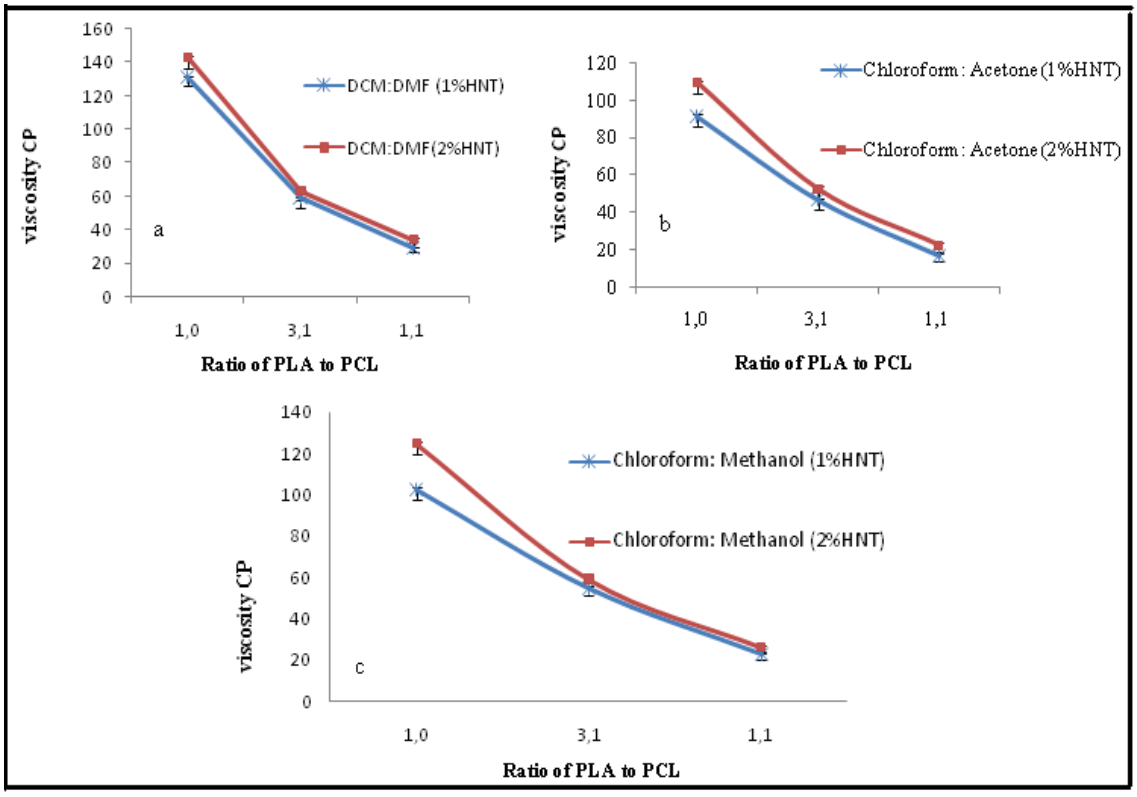

Fig5. Viscosity of different percentage of PLA: PCL solutions dissolved in the mixture of (a) DCM: DMF with HNT (b) chloroform: acetone with HNT (c) chloroform:methanol with HNT.

When compared with samples without HNT loading, Fig6 revealed that using PLA and PLA:PCL blend in chloroform: methanol with HNT produced good fibers in the 450nm range, specially at PLA: PCL (3:1). This is because HNT increases the electrical conductivity and the viscosity of the solution (Touny et al. 2010). In addition, the high volatility of methanol allowed adequate evaporation of the solvent before the deposition

of fibers on the collector plate, leading to the formation of the highly fibrous structure (Jiang et al. 2004). On the other hand, as shown in fig7, electrospun PLA and PLA:PCL blend in DCM:DMF with HNT produced significantly thicker fibers as compared to samples without HNT. This occurred despite an increase in the solution conductivity. During the electrospinning process, it was observed that the solution had flow difficulty due to the high viscosity of the solution, and the electric charge was not able to overcome the increased viscosity leading to a failure in forming a polymer jet (Um et al. 2004). In addition, unlike methanol, the low volatility of DMF led to reduced solvent evaporation leading to fibers that were wet at the collector plate (Hsu et al. 2010). When compared with SEM images of fibers from chloroform: acetone solution, we see that fibers from chloroform: acetone (Fig8) have the smallest diameter, but also they show a greater amount of bead formation. Hence, high conductivity of the solution may not overcome the surface tension and high viscosity of the solution by using a low volatility solvent.

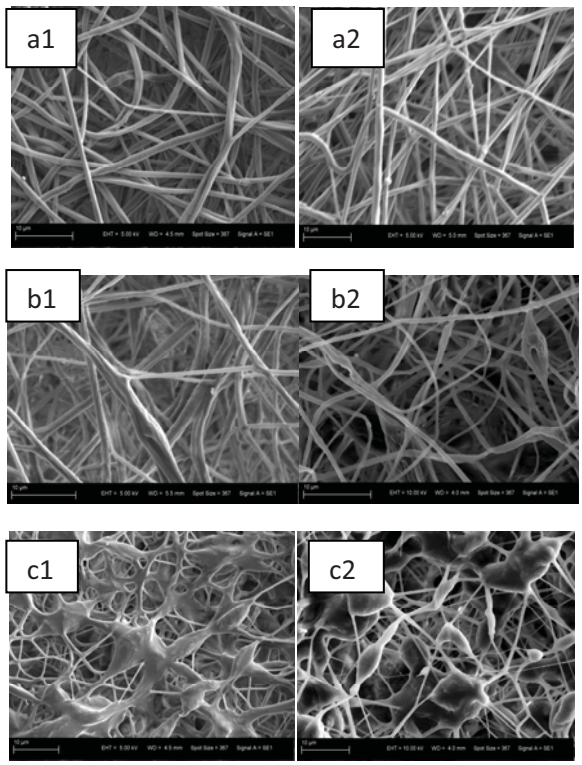

Fig6. SEM micrographs of electrospun PLA: PCL fibers by using chloroform: methanol as a solvent and containing various PLA: PCL blend ratios (a1) 1:0 wt%, (b1) 3:1 wt%, and (c1) 1:1 wt% with 1% wt of HNT and (a2) 1:0 wt%, (b2) 3:1 wt%, and (c2) 1:1 wt% with 2% wt of HNT.

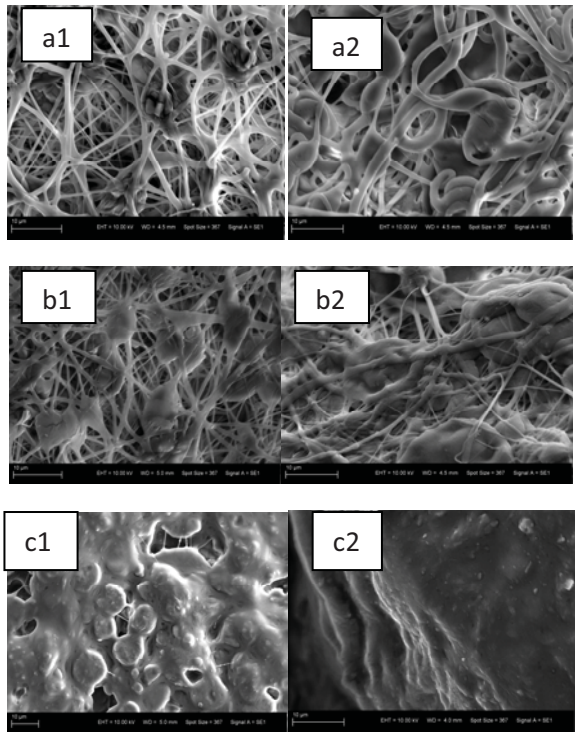

Fig7. SEM micrographs of electrospun PLA: PCL fibers by using DCM: DMF as a solvent and containing various PLA: PCL blend ratios (a1) 1:0 wt%, (b1) 3:1 wt%, and (c1) 1:1 wt% with 1% wt of HNT and (a2) 1:0 wt%, (b2) 3:1 wt%, and (c2) 1:1 wt% with 2% wt of HNT.

Table 3. Summaries the average fiber diameters for all structures with HNT. All fiber diameter are in nm and NA refers to no fiber obtained.

	PLA:PCL (1:0)		PLA:PCL (3:1)		PLA:PCL (1:1)	
	1% HNT	2% HNT	1% HNT	2% HNT	1% HNT	2% HNT
DMF: DCM	950	1100	730	850	NA	NA
chloroform: methanol	970	1050	930	760	600	650
chloroform: acetone	460	500	425	440	400	NA

Thermal properties

The DSC results in table 4 shows that by blending PLA with PCL there was a significant decrease in T_g compared with the fibers produce with PLA addition and blends (About a 20 ^oC reduction), but, there was only a slightly change in T_m. Adding 2% of HNT led to a small decrease in T_g values for PLA:PCL blend nanofibers except for pure PLA in (DSC:DMF) and PLA : PCL with 2% of HNT dissolved in (chloroform: methanol); however, T_m values showed no significant change for most samples. The interesting aspect was the influence of solvents on

the Tg and T_m values of the blends. For example, PLA in (DSC:DMF) showed a T_g of 62.87 °C and T_m of 157.96 °C while, PLA in (chloroform: methanol) showed a T_g value of 66.41 and T_m value of 155.41 °C.

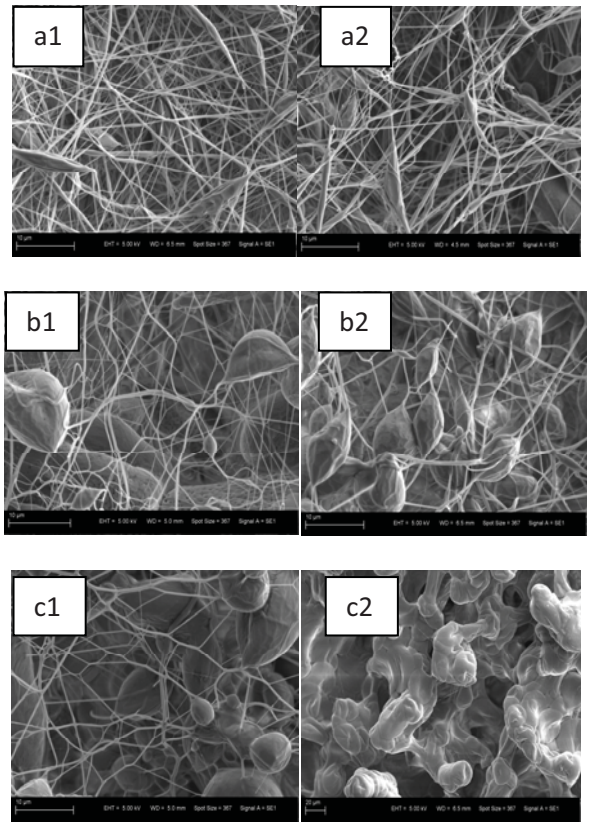

Fig8. SEM micrographs of electrospun PLA: PCL fibers by using Chloroform: Acetone as a solvent and containing various PLA: PCL blend ratios (a1) 1:0 wt%, (b1) 3:1 wt%, and (c1) 1:1 wt% with 1% wt of HNT and (a2) 1:0 wt%, (b2) 3:1 wt%, and (c2) 1:1 wt% with 2% wt of HNT.

Table 4. DSC results for PLA and PLA: PCL nanocomposites with and without HNT and with different co-solvents. Calculation were repeated for 3 sets of samples and standard deviation for the T_g and Tm values are <1%.

Sample	T_g °C	T_m °C	ΔH_m (J/g)
PLA – (DSC:DMF)	62.87	157.96	31.16
PLA – 2%HNT (DSC:DMF)	64.75	155.36	30.9
PLA- chloroform: methanol	66.41	155.41	25.64
PLA- 2% HNT (chloroform: methanol)	58.51	153.91	24.79
PLA- (chloroform: acetone)	63.22	155.16	25.42
PLA- 2% HNT (chloroform: acetone)	58.89	155.12	23.38
PLA : PCL, 3:1, DSC:DMF	46.43	153.93	17.05
PLA : PCL, 3:1, 2% HNT (DSC:DMF)	44.13	153.89	15.23
PLA : PCL, 3:1, (chloroform: methanol)	45.62	154.47	24.57
PLA : PCL, 3:1, 2% HNT (chloroform: methanol)	46.44	154.41	17.15

Conclusion

This study focused on PLA and blends of PLA with low molecular weight PCL reinforced with two different concentration of halloysite nanotubes and different kind of co-solvents for electrospinning. Fiber properties were found to be related to the viscosity and conductivity of the bulk solution. The result shows that increase percentage of PCL led to decrease in the solution viscosities. The fiber produced from the DCM:DMF system without HNT nanoparticles were more uniform resulting in smaller fiber diameters as compared to chloroform:methanol system and this is directly related to the solution conductivity. When HNT nanoparticles are added, It was found that fibers with a large diameter are produced because the viscosity of the solution increased by the addition of HNT. Using PLA and PLA: PCL blend in chloroform:methanol with HNT produced uniform fibers in the 450nm range, specially with PLA: PCL system with polymer ratio of 3:1. This is because HNT not only increases the viscosity but also increases the electrical conductivity of the solution. In addition, the high volatility of methanol allowed adequate evaporation of the solvent leading to production of smaller diameter fibers. Electrospun PLA and PLA: PCL blend in DCM: DMF with HNT produced significantly thicker fibers as compared to samples without HNT and this is attributed to the high viscosity and low volatility of the solvent which negated the effects of higher conductivity of the solution.

References

Bhardwaj, N, and SC Kundu. 2010. Electrospinning: A fascinating fiber fabrication technique. *Biotechnology advances* 28 (3):325-347.

Buschle-Diller, G, J Cooper, Z Xie, Y Wu, J Waldrup, and X Ren. 2007. Release of antibiotics from electrospun bicomponent fibers. *Cellulose* 14 (6):553-562.

Cui, W, X Li, X Zhu, G Yu, S Zhou, and J Weng. 2006. Investigation of drug release and matrix degradation of electrospun poly (DL-lactide) fibers with paracetanol inoculation. *Biomacromolecules* 7 (5):1623-1629.

Fortunati, E, I Armentano, A Iannoni, and JM Kenny. 2010. Development and thermal behaviour of ternary PLA matrix composites. *Polymer Degradation and Stability*.

Han, J, CJ Branford-White, and LM Zhu. 2010. Preparation of poly ([epsilon]-caprolactone)/poly (trimethylene carbonate) blend nanofibers by electrospinning. *Carbohydrate Polymers* 79 (1):214-218.

Han, J, TX Chen, CJ Branford-White, and LM Zhu. 2009. Electrospun shikonin-loaded PCL/PTMC composite fiber mats with potential biomedical applications. *International journal of pharmaceutics* 382 (1-2):215-221.

Heydarkhan-Hagvall, S, K Schenke-Layland, AP Dhanasopon, F Rofail, H Smith, BM Wu, R Shemin, RE Beygui, and WR MacLellan. 2008. Three-dimensional electrospun ECM-based hybrid scaffolds for cardiovascular tissue engineering. *Biomaterials* 29 (19):2907-2914.

Hsu, FY, YS Hung, HM Liou, and CH Shen. 2010. Electrospun hyaluronate-collagen nanofibrous matrix and the effects of varying the concentration of hyaluronate on the characteristics of foreskin fibroblast cells. *Acta biomaterialia* 6 (6):2140-2147.

Jiang, H, D Fang, BS Hsiao, B Chu, and W Chen. 2004. Optimization and characterization of dextran membranes prepared by electrospinning. *Biomacromolecules* 5 (2):326-333.

Kenawy, ER, FI Abdel-Hay, MH El-Newehy, and GE Wnek. 2009. Processing of polymer nanofibers through electrospinning as drug delivery systems. *Materials Chemistry and Physics* 113 (1):296-302.

Kim, K, YK Luu, C Chang, D Fang, BS Hsiao, B Chu, and M Hadjiargyrou. 2004. Incorporation and controlled release of a hydrophilic antibiotic using poly (lactide-co-glycolide)-based electrospun nanofibrous scaffolds. *Journal of Controlled Release* 98 (1):47-56.

Luong-Van, E, L Grøndahl, KN Chua, KW Leong, V Nurcombe, and SM Cool. 2006. Controlled release of heparin from poly ([epsilon]-caprolactone) electrospun fibers. *Biomaterials* 27 (9):2042-2050.

Pham, QP, U Sharma, and AG Mikos. 2006. Electrospinning of polymeric nanofibers for tissue engineering applications: a review. *Tissue engineering* 12 (5):1197-1211.

Touny, AH, JG Lawrence, AD Jones, and SB Bhaduri. 2010. Effect of electrospinning parameters on the characterization of PLA/HNT nanocomposite fibers. *Journal of Materials Research* 25:857-865.

Um, IC, D Fang, BS Hsiao, A Okamoto, and B Chu. 2004. Electro-spinning and electro-blowing of hyaluronic acid. *Biomacromolecules* 5 (4):1428-1436.