Int. J. Electrochem. Sci., 11 **(2016)** 111 - 125

International Journal of
ELECTROCHEMICAL
SCIENCE
www.electrochemsci.org

Determination of Donepezil HCl Release from Electrospun Fiber by Electrochemical Impedance Spectroscopy

Asli Gencturk[1], *A.Sezai Sarac*[1, 2,*]

[1] Polymer Science and Technology, Istanbul Technical University, Maslak, Istanbul, Turkey
[2] Department of Chemistry, Istanbul Technical University, Maslak, Istanbul, Turkey
[*]E-mail: sarac@itu.edu.tr

Received: 9 September 2015 / *Accepted:* 18 October 2015 / *Published:* 1 December 2015

Electrospun fibers of polyurethane [PU] and [PU/HPC] with or without drug loaded were successfully fabricated by electrospinning technique. The structures of the PU/ hydroxypropyl cellulose (HPC) electrospun fiber loaded with Donepezil (DP) were characterized using Fourier Transform Infrared Spectroscopy (FTIR). UV-Visible spectrophotometer and Electrochemical Impedance Spectroscopy (EIS) are used to determine drug release from the electrospun fiber in buffer solution. The electrochemical impedance spectroscopy data were fitted with Electrical Circuit Model of (R(Q(RW))(QR)) which gives a good correlation between the calculated and the experimental values. Electrochemical measurements gave more accurate results according to UV-Visible results for drug release which can be alternative and easy way to determine the drug release from the electrospun fiber. EIS measurements indicated that Warburg Impedance (W) was decreased and charge transfer resistance (Rct_2) was increased according to the increasing of the amount of HPC in the formulation. The morphology of the electrospun fibers indicated that diameters of the electrospun fibers depends on the presence of HPC content and drug molecule.

Keywords: Drug delivery, Electrospinning, Donepezil, Electrochemical impedance

1. INTRODUCTION

Donepezil (DP) is a reversible inhibitor of the enzyme acetylcholinesterase, known chemically as (±)-2,3-dihydro-5,6-dimethoxy2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one. It is selective for acetylcholinesterase rather than butyrylcholinesterase. Donepezil is indicated in patients with mild to moderate Alzheimer's disease [1]. After oral administration of cholinesterase inhibitors the large fluctuations concentration levels in plasma have been associated with high incidence of gastrointestinal adverse effects like diarrhea, nausea, and vomitin [2].

Electrospun nanofibers are promising candidates in the nanotechnological applications due to their potential applications for biomedical devices, tissue engineering, and drug delivery carriers electrospun fibers which has a high surface area to volume ratio have received much attention. The main advantages of electrospun fibers as drug delivery carriers are that they offer site-spesific delivery of drugs to the body and exhibit a great surface area that could allow drug molecules to diffuse out of matrix readily due to the highly porous structure [3]. Vrbata [4] and coworkers studied in vitro dissolution of diosmin, three different forms like powdered drug, micronized diosmin powder (commercially available tablets), and diosmin loaded nanofibrous membranes. On the contrary to the powder or micronized form, the nanofibrous membrane carrier provided about 70% of the incorporated drug dissolved in the release medium.

Polyurethanes have suitable mechanical properties and good biocompatibility because of that they are regarded as an excellent biomaterials [5–9] Resistant polyurethanes have found a wide application area as long term implant materials, artificial heart valves, wound dressings, angioplasty balloons, ventricular assist devices, and pacing lead insulation [10-11] Recently, Tyrosinase (Tyr) was covalently immobilized onto polyacrylonitrile/ polyurethane/ poly(m-anthranilic acid) (PAN/PU/P3ANA) nanofibers [12] and PCL/PPy electrospun nanofiber mat was found suitable for DNA immobilization and characterized the interaction between DNA and nanofibers by means of electrochemical impedance spectroscopy [13].

Hydroxypropylcellulose (HPC) is a biodegradable polymer which has been extensively used in the fields of tissue engineering and pharmacy [14–16]. HPC can be favorable in biomedical or wound healing application if they can be formed into fiber-like or sheet structures. Electrospinning makes it possible to produce such nanofibrous membranes having submicronic interconnected pore like structure in a cost-effective manner [17-18].

Hydroxypropylcellulose (HPC) has been frequently utilized as a pharmaceutical additive for various purposes as a binder in tablet or granule formulations, a film-coating material. Also, controlled release dosage forms [19] or bioadhesive tablets [20] have been prepared utilizing its swelling and adhesive properties in aqueous medium.

During the recent years, the electrochemical techniques have become advantageous because they exhibit short analysis time, low limits of detection, low cost, less time consuming and more selective if it is compared the other techniques [21]. Because the traditional methods generally suffer from the disadvantages of expensive instrument, specific signal reporters, cumbersome and time-consuming assay procedures. Thus, the development of convenient detection of drug is highly desirable. These studies found many applications area like drug analysis in their dosage forms and especially in biological samples. A wide range of analytical techniques are available to determine donepezil present in samples [22–25]. Liquid chromatographic and UV spectrophotometric methods were used to estimate of donepezil hydrochloride in tablet and bulk formation [26-27]. Electroanalytical determination of donepezil hydrochloride in tablets and human serum by differential pulse and square wave voltammetry was performed at a glassy carbon electrode [28]. Also it was examined at a gold electrode using cyclic voltammetry (CV) [29].

The main objective of this study was to develop a drug release system from polyurethane (PU) / hydroxypropyl cellulose (HPC) fiber by using electrospinning method and to find an alternative way

to determine donepezil molecule in the solution. UV-vis spectroscopy which is the most common method for spectroscopic detection, electrochemical impedance measurement and electric circuit model which have not been explored before, were used to evaluate the drug release profiles. So, we have used impedance and electrical circuit model as a detection method in this study. Ariffin [30] has been reported the detection of Hydrogen Peroxide and Ascorbic Acid using modified electrode by EIS. These different techniques which are electrochemical impedance measurement and electric circuit model have been introduced as an alternative approach to determine donepezil for the drug release system. Also spectroscopic and morphological measurement were used to investigate the effect of the HPC content on the resulting electrospun fibers.

2. EXPERIMENTAL

2.1. Materials

Thermoplastic PU was supplied from Flokser Co., Istanbul, Turkey. The molecular weight of the PU is 93,000 g/mol. Hydroxypropylcellulose (HPC) with an molecular weight (Mw) of 140,000 (Nippon Soda Co. Ltd) apparent viscosity 8.6 mpa.s (%2 aqua solution at 20^{o}C), assay for hydroxypropoxy group %71.4. N,N-dimethylformamide (DMF) was obtained from Labkim. All the compounds were of analytical grade. Potassium dihydrogen phosphate (KH_2PO_4) was provided by Riedel-de Haën. Sodium hydroxide (NaOH) was provided by Sigma–Aldrich. Indium Tin Oxide coated PET Electrodes (ITO-PET) (Surface Resistivity: 60 Ω/sq) were purchased from Aldrich. The diameter of the working electrode results in a geometric area of 3 cm^2.

2.2. Fourier Transform Infrared Spectroscopy (FTIR)

IR spectroscopic measurements were carried out using the ATR-FTIR reflectance spectrometer (Perkin Elmer, spectrum One; with a universal ATR attachment with a diamond and ZnSe crystal C70951)

2.3. UV-Visible Spectroscopy

The absorbance of standard Donepezil HCl solutions with different concentrations were measured using Shimadzu UV–VIS 1500 Spectrophotometer, at 229 nm, and the calibration curve was constructed. The release of drug in solution was quantified using Shimadzu UV-VIS.

2.4. Preparation of electrospun based ITOPET electrode for EIS measurements

0.5 g of PU was dissolved in DMF (4 ml) to prepare the electrospinning solutions. Homogeneous and clear polymer solutions were prepared by stirring PU in DMF for 4 h at room temperature. Donepezil HCl was added to one of the homogeneous polymer solutions and stirred for 30 minutes. Sample was coded by A1. Also a different amount of HPC was added to the homogeneous

polyurethane solutions to get composite solutions. Composite solutions (include % 25 HPC, % 50 HPC and % 75 HPC) were stirred for 15 minutes for getting clear solution. Donepezil HCl was added to these homogeneous polymer solutions and stirred for 30 minutes. Sample was coded by A2-A4 respectively.

The electrospinning apparatus consisted of a syringe pump (NE-500 Model, New Era Pump Systems, Inc. USA) with a feeding rate from 5.5 μL/h to 400 mL/h, a high voltage direct current (DC) power supplier generating positive DC voltage up to 50 kV DC power supply (ES 30 Model, Gamma High Voltage Inc., USA), and a grounded collector that was aluminum. The solutions (A1-A4) which were electrospun horizontally on to the aluminum collector were loaded into a syringe and a positive electrode was clipped onto the syringe needle.Syringe needle had an outer diameter of 0.8x38 mm. The feeding rate of the polymer solution was controlled by a syringe pump which was set at a volume flow rate of 1 mL/h. The applied voltage was 15 kV, the tip-to-collector distance was 15 cm, and all solution preparations and electrospinning were carried out at room temperature.

ITOPET sheets which were cut in a rectangular shaped (1-4 cm size) fixed on aluminum collector and were coated with A1-A4 (prepared according to content of Table 2) sample solutions by electrospinning process. Coated ITOPET ([PU/HPC] electrospun fiber loaded Donepezil HCl) was dipped into the 5 ml isotonic pH 6.5 phosphate buffer (di-Sodium hydrogen phosphate/ Potassium dihydrogen phosphate) solution. EIS was measured in predetermined time intervals (15th, 30th, 45th, 60th, 90th, 120th and 180th minute) in buffer solution at room temperature. ITOPET electrode coated with electrospun fiber was used as a working electrode, Pt was used as a counter and Ag was used as a reference electrode in EIS measurement. After EIS measurement, Donepezil HCl amounts are calculated with UV Visible spectroscopy.

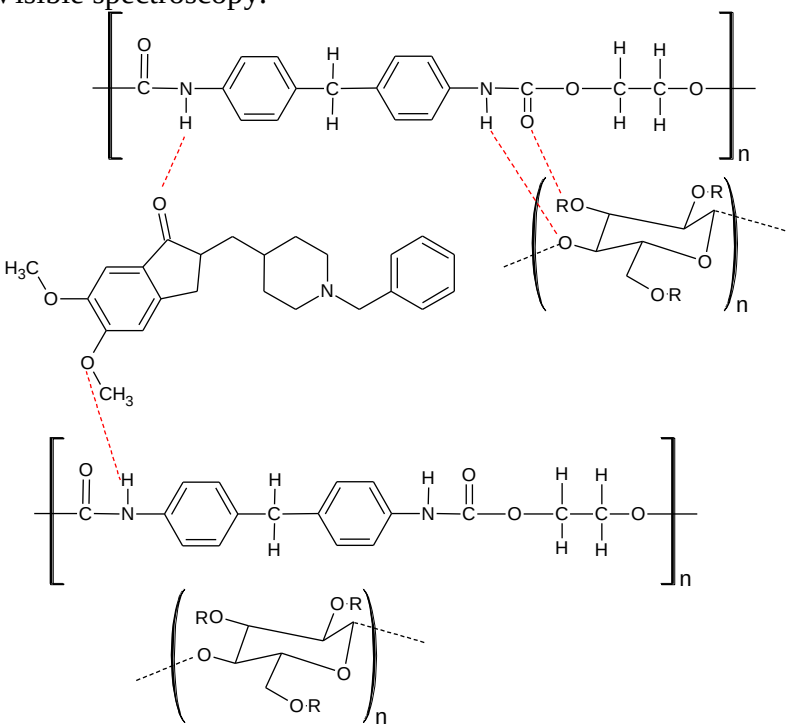

Figure 1. Schematic tentative illustrations of the interaction between PU, HPC and Donepezil

3. RESULTS AND DISCUSSION

3.1. ATR-FTIR Spectrophotometric Characterization of Electrospunfibers

Infrared spectra were measured with an ATR-FTIR reflectance spectrometer in the wavenumber range 800–4000 cm^{-1}.

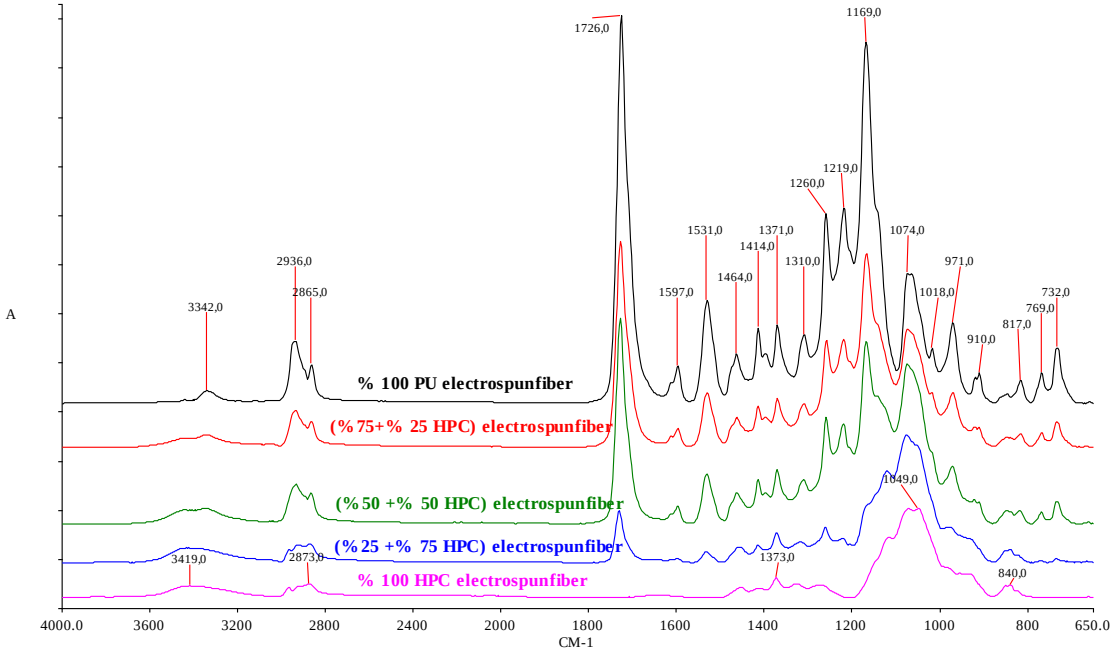

Figure 2. FTIR-ATR Spectrum of [PU/HPC] electrospun fibers with different content of PU/HPC

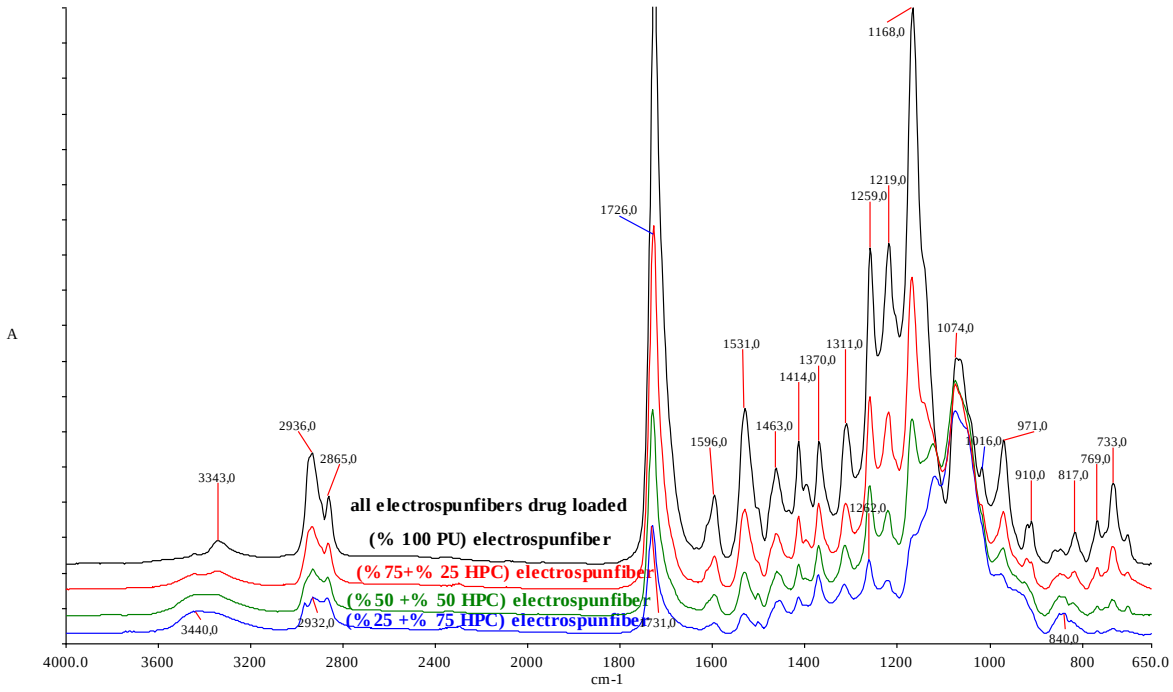

Figure 3. FTIR-ATR Spectrum of Donepezil HCl loaded electrospun fibers with different content of [PU/HPC]

Characteristic absorption bands related to polyurethanes can be observed in Figure 2, such as: the 1726 cm^{-1} band, due to the carbonyl groups in urethane bonds (C=O); the 1531 cm^{-1} band, usually assigned to secondary amide (RCONHR'); the 1597 cm^{-1} band, assigned to carbonyl groups (C=O) in urea bond; the 1260-1219 cm^{-1} and 1169 cm^{-1} band due to C-O stretch and C-N stretch; the 3342 cm^{-1} and 2936 cm^{-1} bands from N-H and C-H groups.

Hydroxypropyl cellulose is a water soluble polymer, which exhibits relatively numerous hydroxyl functional groups active in hydrogen bonding. The ATR-FTIR absorbance of the hydroxypropyl cellulose is related by the stretching vibrations of the –OH groups located at 3600–3100 cm^{-1}, with a maximum at 3419 cm^{-1}, by the stretching vibrations ν(C-O-C) groups located at 1049 cm^{-1} and the bands corresponding to aliphatic groups located at 2873 cm^{-1} in Figure 2.

The ATR-FTIR of the polyurethanes, HPC and polyurethanes with HPC the stretching vibration (N-H) peak migrated from 3419 cm^{-1} to 3342 cm^{-1} and broad peaks convert into narrow peak because of the stronger hydrogen bonded urethanes increases with the increasing PU content.

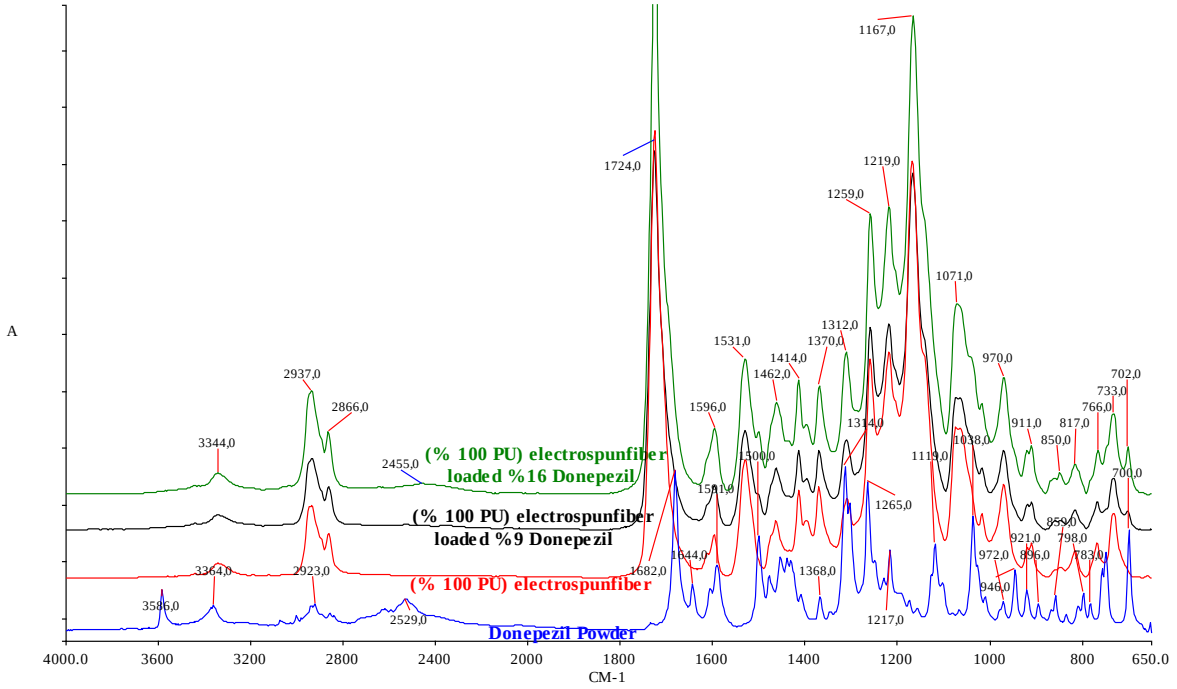

Figure 4. FTIR-ATR Spectrum of Donepezil HCl and Donepezil HCl loaded [PU] electrospun fibers

The FTIR spectra of the Donepezil HCl (pure drug), PU electrospun fiber with Donepezil loaded (%9 and %16Donepezil (the drug was hardly soluble in the liquid polymer system at this concentration) or Donepezil free are presented in Figure 4. From the spectra of the Donepezil HCl, it was observed that the main functional groups of the compound are aromatic phenone and para-substituted aromatic hydrocarbon. The most intensive absorption band around 1682 cm^{-1} in the spectra was attributed to the stretching vibrations of C=O group in the structure of Donepezil HCl (31). This sharp peak indicated the presence of aromatic phenone ring in the compound. Absorption band around

1591 cm^{-1} indicated the presence of C=C stretching in the compound. The sharp absorption band at 1312 cm^{-1} or 1314 cm^{-1} indicated the presence of C–N bond in the structure (32). 748 and 700 cm^{-1} indicated the presence of aromatic C-H bending in the structure.

3.2. Determination of drug release from Donepezil HCl loaded [PU/HPC] electrospunfibers by UV-Visible Spectroscopy

Electrospun based ITOPETs (sample A1-A4) with Donepezil HCl loaded were dipped into the 5 ml isotonic pH 6.5 phosphate buffer (di-Sodium hydrogen phosphate/ Potassium dihydrogen phosphate) solution and in predetermined time intervals (15^{th}, 30^{th}, 45^{th}, 60^{th}, 90^{th}, 120^{th} and 180^{th} minute) solutions were taken for UV-Vis measurement and drug released from the electrospun fiber was measured by UV Visible spectroscopy which were scanned in spectrum mode between 500 to 200 nm to determine λ max. The results of absorbance were taken and plotted against time to absorbance. Figure 5 shows the UV absorption spectrum of Donepezil HCl released from A2 (sample code) electrospun fiber. It shows maximal peak at 229 nm, and two smaller maxima at wavelengths of 270 nm, and 314 nm (270 nm was used as detection wavelength). When A1 (100% PU) sample was immersed to buffer solution, it started to strip from the surface of ITOPET after 30^{th} minutes. Spectroscopic results of A1 were not taken after 30^{th}. But striping was not seen at the other samples which is included HPC. Added HPC for controlled release is also known as a bioadhesive polymer. This feature of HPC allows to electrospun fibers to grip tightly on ITOPET.

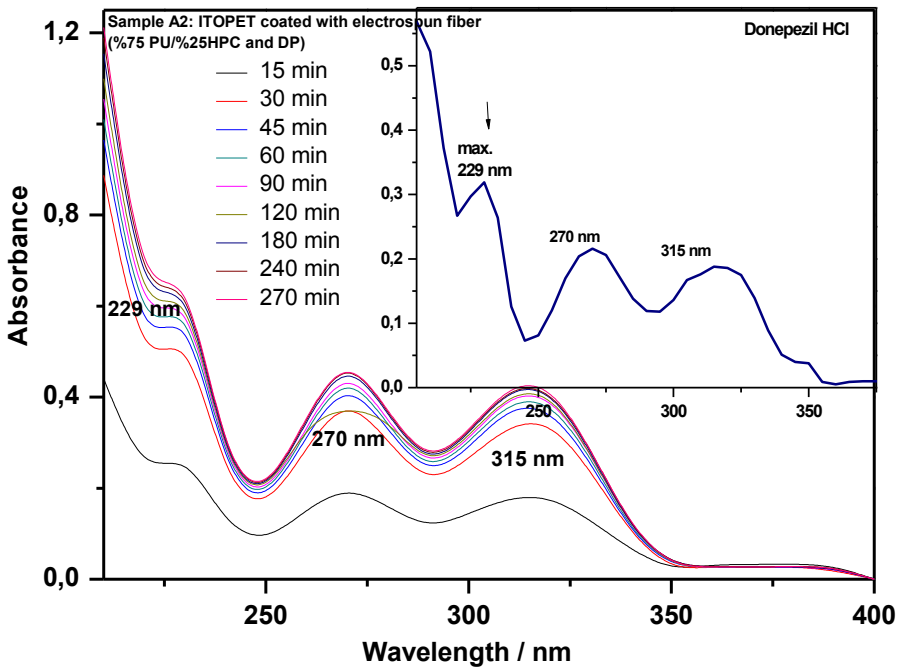

Figure 5. The UV absorptions maxima of Donepezil HCl released from ITOPET coated with electrospun fiber after different time intervals

3.3. Determination of drug release from Donepezil HCl loaded [PU/HPC] electrospun fibers by Electrochemical Impedance Spectroscopy and Equivalanet Circuit Modelling

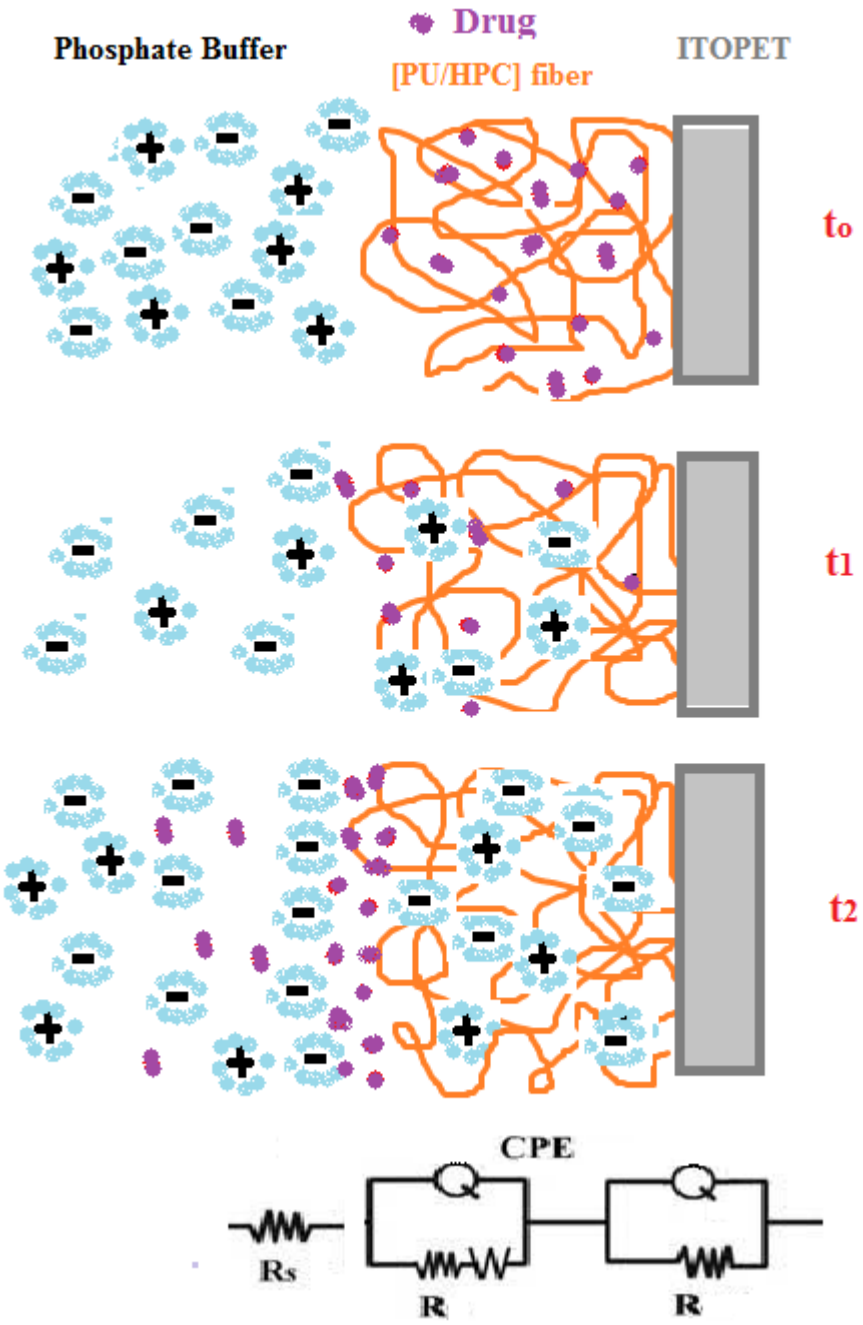

Figure 6. Equivalent electrical circuit model for the simulation of the EIS spectra of drug loaded [PU/HPC] electrospun fibers and drug release (t_o: the first moment when the fiber is immersed into the solution, t_1: the buffer solution is started to penetrate into the fiber, drug release is started, t_2: the buffer solution is penetrated into the fiber and drug release occurred).

Electrochemical Impedance Spectroscopy is a technique which infers more information on the electrochemical interfacial properties of surface-modified electrodes by providing electrical parameters, such as double layer capacitance (Cdl), Warburg impedance (infinite diffusion, W),

transfer resistance (Rct), solution resistance (Rs), and diffusion coefficient [33-34]. EIS allows to evaluate the electrical properties of electrospun nanofibers based on ITOPET and the drug release from the electrospun fibers. There are few reports in the literature on the determination of biological molecule using EIS and electrical circuit model in bioelectrochemical systems [35]. Electrospun based ITOPET (sample A1-A4) with Donepezil HCl loaded was dipped into the 5 ml isotonic pH 6.5 phosphate buffer (di-Sodium hydrogen phosphate/ Potassium dihydrogen phosphate) solution. Electrospun based ITOPET was used as a working electrode, Pt was used as a counter and Ag was used as a reference electrode in electrochemical impedance spectroscopic measurements. Electrochemical impedance spectroscopic (EIS) measurements were realized in predetermined time intervals (15^{th}, 30^{th}, 45^{th}, 60^{th}, 90^{th}, 120^{th} and 180^{th} minute) in buffer solution at room temperature.

The best fit between model and experimental data was achieved by using the equivalent circuit shown in Figure 6 in order to characterize the electrochemical properties of ITOPET coated with electrospun fiber. The analysis and model fitting using Z Simp Win software of the Nyquist plot (Z' vs. Z") has been shown in Figure 7. The impedance spectra for electrospun fibers described by the equivalent circuit of (R(Q(RW))(QR)). The proposed model contains resistance of the electrolyte, Rs, constant phase element, Q, R_{ct} charge transfer resistance (or polarization resistance), Warburg Impedance, W. The first component contains the solution resistance of the electrolyte, Rs. The second component contains the paralel combination of the constant phase element, Q used to represent the CPE, and the charge transfer resistance between the electrospun fiber and the buffer solution interface, Rct_1 and the series connection to Rct was the Warburg Impedance, W for diffusion of drug species at the interface. The third one contains constant phase element, Q which was parallel combination of the third resistance is between the electrofiber and ITOPET electrode, Rct_2.

Table 1. Parameters obtained from the fitting of impedance data with equivalent circuit model for the Donepezil HCl loaded A1-A4 sample (released at 15^{th} minutes)

	Sample Code				
MODEL	Bare ITOPET	A1 (0% HPC)	A2 (25 % HPC)	A3 (50 % HPC)	A4 (75 % HPC)
R_S [Ω]	342.2	254.4	251.5	241.0	224.4
CPE (10^{-5}) [Y_0/Ss^{-n}]	1.20	2.42	2.01	2.56	1.49
n	0.93	0.95	0.93	0.93	0.94
Rct_1 [Ω]	$35.25E^{4}$	57.48	$3.00E^{14}$	$26.86E^{-3}$	$3.46E^{5}$
W [Y_0/Ss^{-n}]	$8.17E^{-7}$	$3.57E^{-6}$	$6.31E^{-13}$	$2.92E^{-20}$	$5.52E^{-7}$
CPE (10^{-5}) [Y_0/Ss^{-n}]	4.19	$8.63E^{-2}$	50.71	9.40	12.03
n	0.61	0.57	0.81	0.91	0.71
Rct_2 [Ω]	129.9	346.3	368.7	815.2	9.3
Chi Squared	$3.58\ E^{-4}$	$5.92\ E^{-5}$	$1.44\ E^{-4}$	$1.47\ E^{-4}$	$1.37\ E^{-4}$

Values for Rs did not vary significantly. Warburg Impedance, W values are $3, 57E^{-6}$, $6, 31E^{-13}$, $2, 92E^{-20}$ for A1, A2, A3 samples respectively shown in Table 1 and 2. A3 sample comprises more HPC than A2 and A1. Therefore, Warburg Impedance (W) is decreases according to the increasing of

the amount of HPC. Release profile from the electrospun fiber takes place by combination of the some processes: Water diffuses into the electrospun fiber, swells the HPC. HPC rapidly form a gel layer upon contact with water. The gel layer retards release of the active ingredient, either by diffusion or erosion. Diffusion of drug species at the interface decrease but charge transfer resistance (R_{ct2}) increases (A1: 346.3-A2: 368.7-A3:815.2) with the increase amount of HPC.

Table 2. Table of Z_{RE} absorbance and Warburg Impedance for A1-A4 samples at 15th minutes

Sample Code	% PU	% HPC	Donepezil HCl (g)	Z_{RE} (kOhm) at 10 mHz (for 15th minute)	Absorbance at 270 nm (for 15th minute)	W [Y_0/Ss^{-n}] (for 15th minute)
A1	100	0	0.05	43.92	2.17	$3.57E^{-6}$
A2	75	25	0.05	73.77	0.21	$6.31E^{-13}$
A3	50	50	0.05	62.19	0.61	$2.92E^{-20}$
A4	25	75	0.05	124.00	0.45	$5.52E^{-7}$

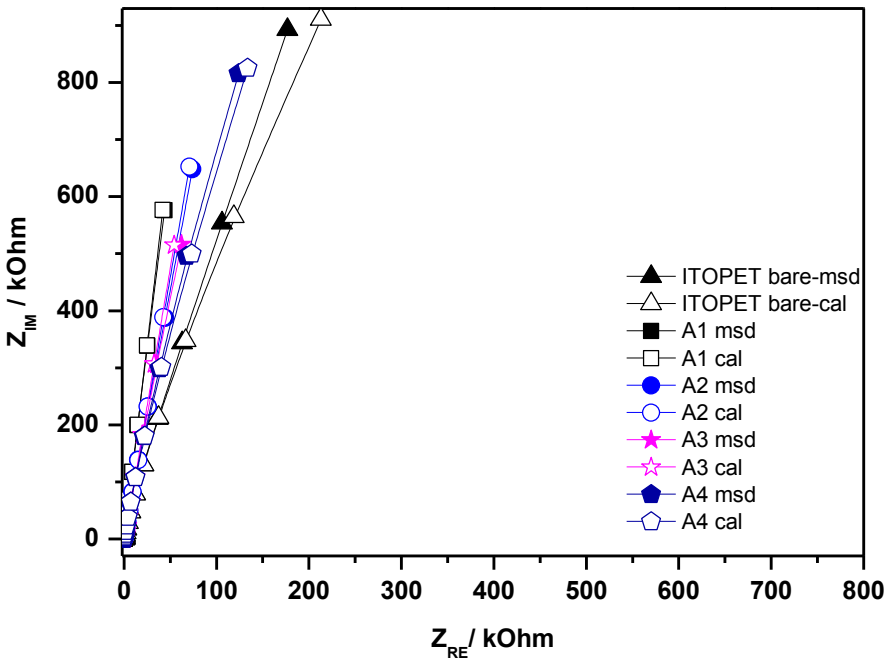

Figure 7. Electrochemical analysis and model fitting of Nyquist plots

Electrochemical properties of blend nanofibers have been characterized with an equivalent electrical circuit model .The Nyquist, Bode Magnitude and Bode Phase plots of the fibers were given in the frequency range 0.01 Hz–100 kHz (Figure 7). Calculated data and measured data which were best fitted with the proposed model is shown in Figure 7 and 8. A1 sample is more capacitive than A2, A3 and A4 (Figure 7). It is seen from the Figure 7 that electrospun based ITOPETs are more capacitive than the bare ITOPET.

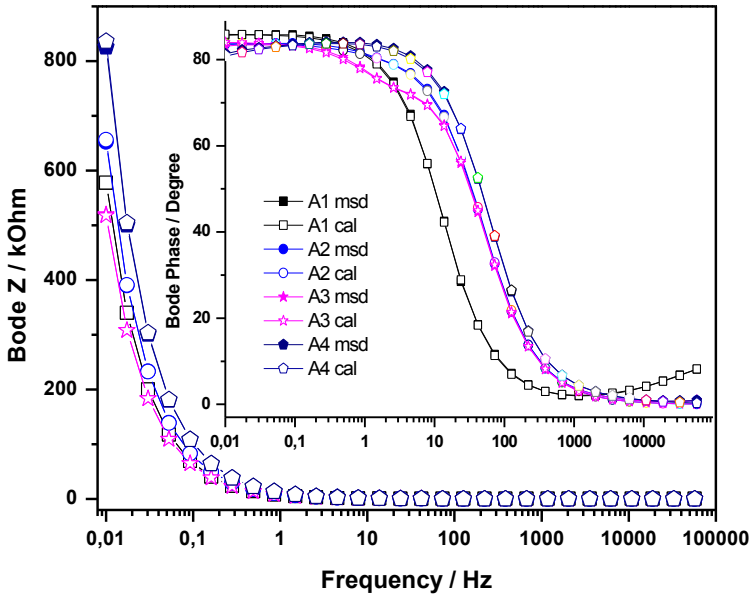

Figure 8. Electrochemical analysis and model fitting of Bode Phase (inset) and Bode Magnitude plots

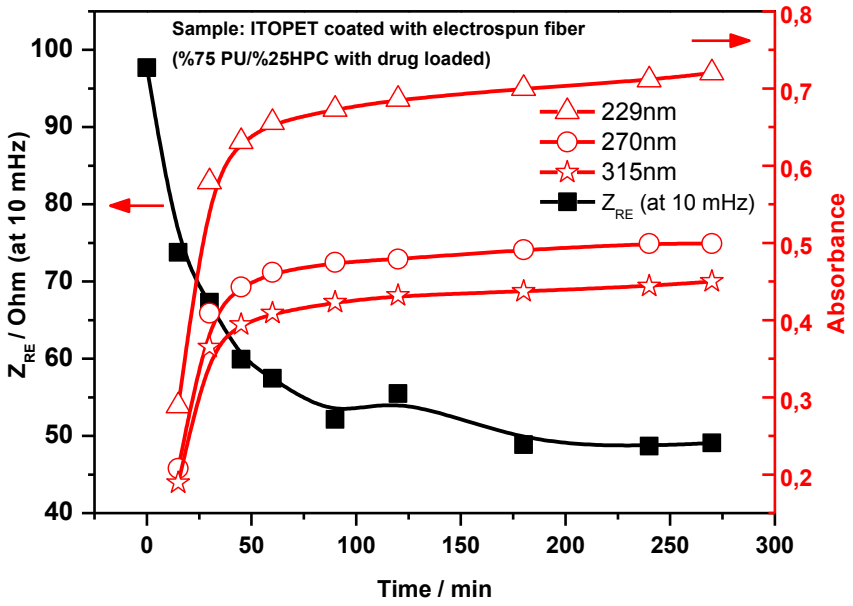

Figure 9. Curve of Z_{RE} (from the EIS data at 10 mHz) and absorbance data versus time for A2 sample

The correlation between Z_{RE} (at 10 mHz) and absorbance versus time for A2 sample is presented in Figure 9. It was found that with the increase in the donepezil concentration the Z_{RE} decreases. When drug molecules were released from the electrospun fiber in the buffer solution as time goes, Z_{RE} results decrease while increasing absorbance values. Because while the amount of the drug molecules in buffer solution increases, the conductivity of the solution also increases and the resistance decreases. R_{CT} increases with the increasing of HPC content in the electrospun fiber in Figure 10.

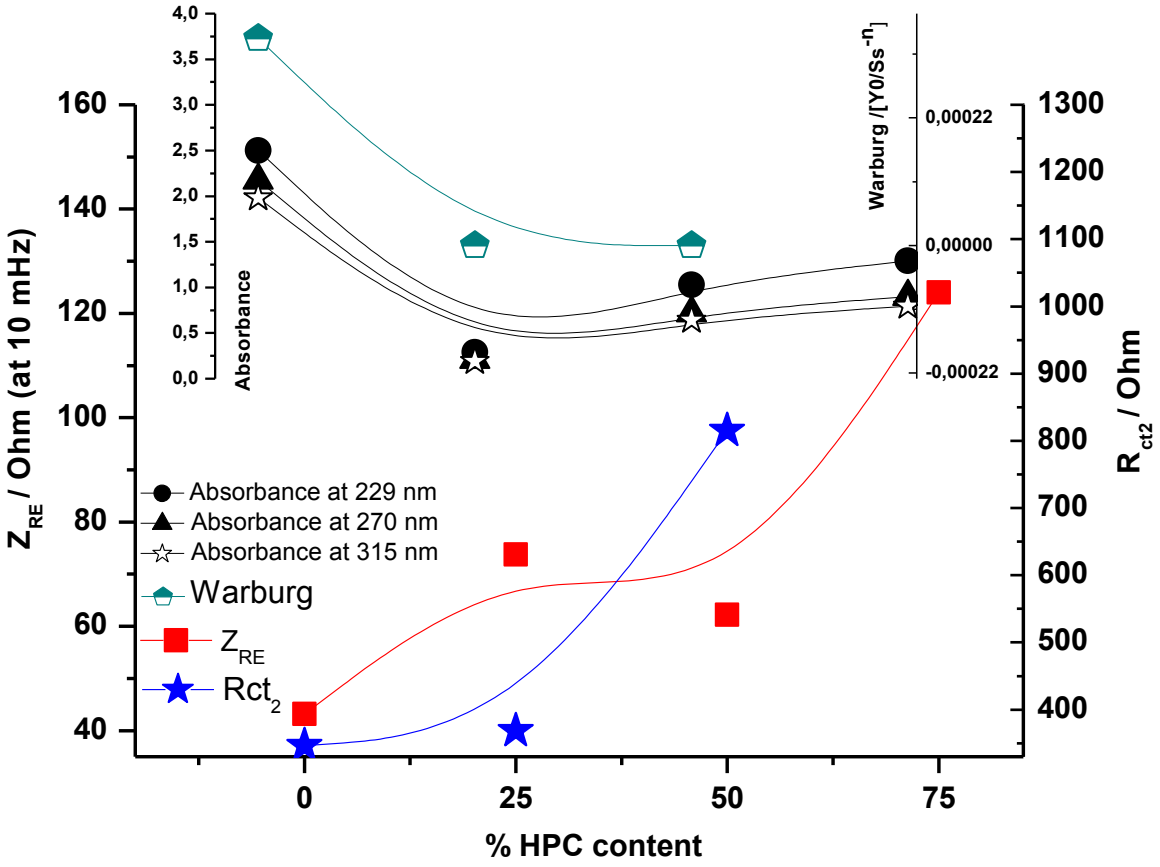

Figure 10. Changes of Z_{RE} (at 10 mHz) and absorbance (at 229 nm, 270 nm, 310 nm) versus % HPC content for the release at 15th min.

3.4. Morphology of Drug Loaded Electrospun Fibers

The average diameter, uniformity of the membrane fiber, effect of donepezil molecule and HPC content on the electrospun fiber were analysedby SEM observation of the cross section of electrospun fiber for [PU] and [PU/HPC] electrospun fibers (no HPC and 10, 16, 25, 45 and 50 % w/w HPC included ones) with drug free and drug loaded samples. in Figure 11. When the concentration of HPC reaches a critical concentration, polymers could entangle in chains, forming large particles, explaining the difficultly in electrospinning [36]. Studies have shown [37] that HPC molecules have strong tendency to form bigger particles. Also, the solution was highly viscous and difficult to electrospin at the critical concentration value. The measurement confirmed that increasing the HPC concentration at the resultant PU with HPC polymeric solution has high viscosity than that of pure PU solution. Studies demonstrated that the viscosity is the critical parameter for the elecrospinning method. Fong et al. [38] demonstrated that the polymer solution with low viscosity results in the formation of the beads caused by the capillary breakup of the jet during the electrospinning due to surface tension HPC solution.

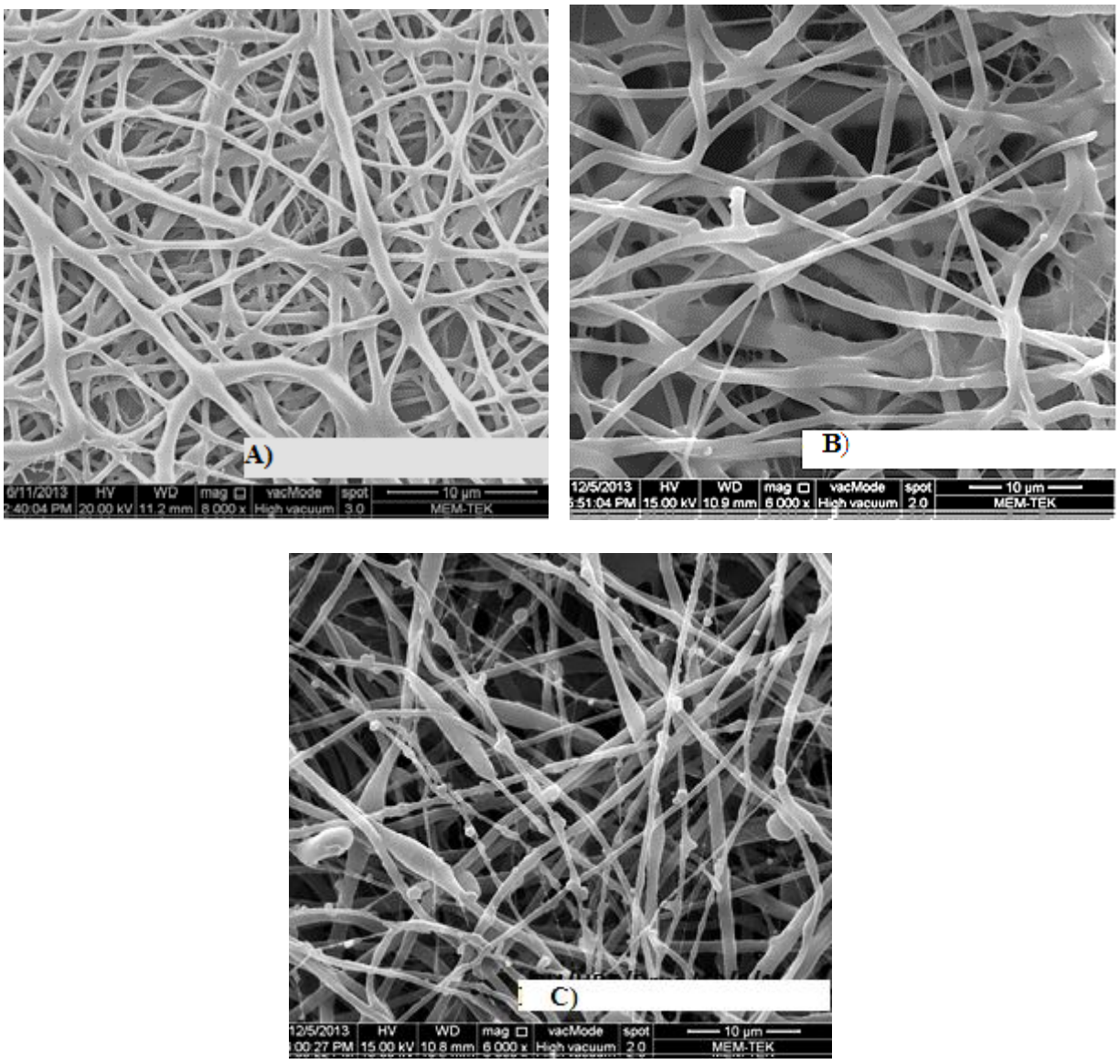

Figure 11. SEM images of [PU] and [PU/HPC] electrospunfibers with drug loaded a) no HPC b) include % 16 HPC c) include % 45 HPC at different magnification.

Figure 12 shows concentration effect of the HPC on the diameters of PU electrospun fibers. Submicron PU/HPC fibers were synthesized between 600 and 1200 nm diameter [39] Increasing of HPC content in PU electrospun fibers, fiber diameter of the electrospun fiber decreases at the drug free electrospun fiber. Similar to the unloaded drug electrospun fiber, the average diameter of fiber decreases with increasing HPC in drug loaded electrospun fiber (Figure 12). Also if we compare the average fiber diameter with loaded and unloaded drug, diameter of the fiber loaded the drug are even smaller (inset of the Figure 12). The obtained results show that the presence of HPC and drug in the electrospun fiber affects the resulting diameter.

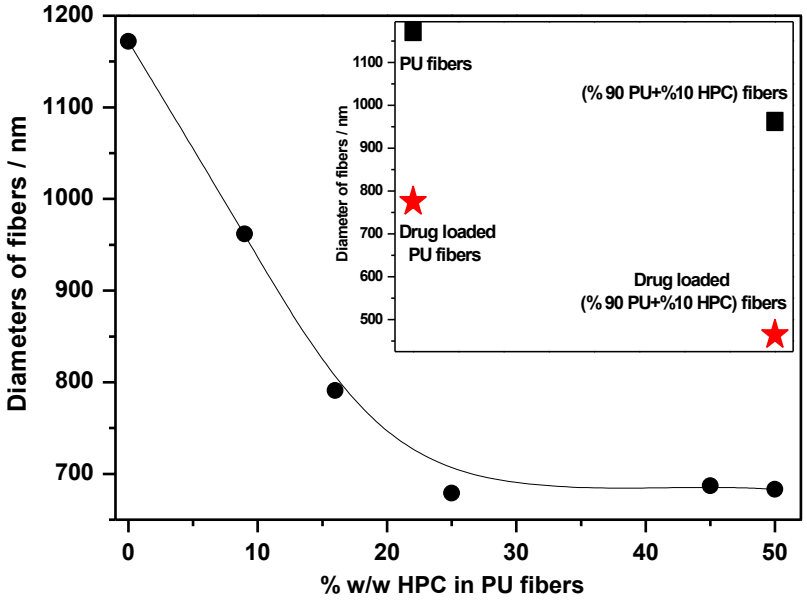

Figure 12. Effect of the concentration of HPC on the diameters of PU fibers (inset: Effect of the Donepezil HCl on the diameters of electrospun fibers).

4. CONCLUSION

In this study; donepezil-loaded or unloaded electrospun fibers of [PU] and [PU/HPC] were successfully formulated by an electrospinning method which allows increasing the dissolution more effectively, owing to the formed huge surface area, tunable porosity and had the ability to adjust fiber composition in order to get desired properties.. Incorporation of Donepezil inside the PU, HPC electrospun fiber were confirmed by FTIR-ATR. Electrochemical impedance spectroscopy, Electrical Circuit Model and UV-Visible spectroscopic approach are used to determine the donepezil release from the electrospun fiber in buffer solution. Electrochemical measurements gave more accurate results compared to UV-Visible results for drug release. EIS measurements indicated that Warburg Impedance (W) was decreased and charge transfer resistance (R_{ct2}) was increased according to the increasing of the amount of HPC in the formulation. The morphology of the electrospun fibers indicated that diameters of the electrospun fibers depends on the presence of HPC content and drug molecule. The obtained data represent the EIS can be an alternative way to determine the drug release from the electrospun fiber in the buffer solution.

References

1. S.L. Rogers and L.T. Friedhoff, *Dementia and Geriatric Cognitive Disord.*, 7 (1996) 293-303
2. B.P. Imbimbo, *CNS Drugs*, 15 (2001) 375.
3. E. Luong-Van, L. Grøndahl, K.N. Chua, K.W. Leong, V. Nurcombe and S.M. Cool, *Biomater.*, *27*.9 (2006) 2042.
4. P. Vrbata, P. Berka, Denisa Stránská, P. Doležal and M. Láznícek, *Int. J. Pharm.*, 473(1), 407.
5. C.J. Spaans, V.W. Belgraver and A.J. Pennings, *J Mater. Sci.: Mater Med.*, 9.12 (1998) 675.
6. G.M.R. Wetzel's, L.H. Koole, J. *Biomater.*, 20 (1999) 1879.

7. K. Gorna, S. Gogolewski, *Polym. Degrad. Stab.*, 79 (2003) 475.
8. I. Khan, N. Smith, E. Jones, D.S. Finch and R.E. Cameron, *Biomater.*, 26.6 (2005) 633.
9. A. Simmons, J. Hyvarinen, R.A. Odell, D.J. Martin, P.A. Gunatillake, K.R. Noble and L.A. Poole-Warren, *Biomater.*, 25.20 (2004) 4887.
10. J.H. Park, Y.W. Cho, I.C. Kwon, S.Y. Jeong, Y.H. Bae, *Biomater.*, 23 (2002) 3991.
11. K. Stokesa and K. Cobiana, *Biomater.*, 3 (1982) 225.
12. A. S. Sarac, U. Dagli, Z. Guler, *Polym. Plast. Technol. Eng.*, (DOI: 10.1080/03602559.2015. 1010218)
13. Z. Guler, P. Erkoc and A. S. Sarac, *Mater. Express*, 5(4) (2015) 269.
14. Z. Ziyan, Z. Hua, W. Ming, H. Jin, C. Yun, *J. Appl. Polym. Sci.*, 107 (2008) 3267.
15. C. Depu and S. Baoquan. *Mat. Sci. Eng. C*, 11 (2000) 57.
16. G.W. Skinner, W.W. Harcum, P.E. Barnum and J.H. Guo, *Drug Dev. Ind. Pharm.*, 25.10 (1999) 1121.
17. Z.M. Huang, Y.Z. Zhang, M. Kotaki and S. Ramakrishna, *Compos. Sci. Technol.*, 63 (2003) 2223.
18. Y. Wang, R. Furlan, I. Ramos and J.J. Santiago-Aviles, *Appl. Phys. A.*, 78.7 (2004) 1043.
19. M. Nakano, N. Ohmori, A. Ogata, K. Sugimoto, Y. Tobino, R. Iwaoku and K. Juni, *J. Pharm. Sci.*, 72.4 (1983) 378.
20. K. Satoh, K. Takayama, Y. Machida, Y. Suzuki, M. Nakagaki and T. Nagai, *Bull. Chem. Pharm.*, 37.5 (1989) 1366.
21. Z. Gao, K.S. Siow, A. Ng and Y. Zhang, *Anal. Chim. Acta*, 343.1 (1997) 49.
22. J. Haginaka and C. Seyama, *J. Chromatogr*., 577 (1992) 95.
23. K. Matsui, Y. Oda, H. Ohe, S. Tanaka and N. Asakawa, *J. Chromatogr. A*, 694 (1995) 209.
24. P.J. Tiseo, K. Foley and L.T. Friedhoff, *Br. J. Clin. Pharmacol*., 46 (1998) 35.
25. K. Matsui, Y. Oda, S. Tanaka and T. Yoshimura, *J. Chrom. Biom. Appl.*, 729 (1999) 147.
26. J. Sangshetti, P. Mahaparale, S. Paramane and D. B.N.R. Shinde, *Trends Appl. Sci. Res.*, 3 (2008) 109.
27. U.K. Chhalotiya, K.K Bhatt, D. A. Shah, and C. D. Nagda, *Int. J. Chem. Tech. Res.*, 3.1 (2011) 112
28. A. Golcu and S. A. Ozkan, Die *Pharmazie-Int. J. Pharm. Sci.*, 61 (2006) 760.
29. A.R. Mladenović, D. Ž. Mijin, S.Ž. Drmanić, V.E. Vajs, V.M. Jovanović, S.D. Petrović and M.L. A. Ivić, *Electroanalysis*, 26.5 (2014) 893.
30. A.A. Ariffin, R.D. O'Neill, M.Z.A. Yahya and Z.M. Zain, *Int. J. Electrochem. Sci.*, 7 (2012) 10154.
31. T.J. Park, D.H. Ko, Y.J. Kim and Y.G. Kim. *Bull. Kor. Chem. Soc.*, 30.9 (2009) 2007.
32. K.K. Reddy, J.M. Babu, P.A. Kumar, E. R. R. Chandrashekar, V.T. Mathad, S. Eswaraiah and K. Vyas, *J. Pharm. Biomed.*, 35.5 (2004) 1047.
33. M. Ates, *Prog. Org. Coat.*, 71 (2011) 1.
34. S. Bason, Y. Oren and V. Freger, *J. Membrane Sci.*, 302 (2007) 10.
35. S. Jung, *Int. J. Electrochem. Sci.*, 7.11 (2012) 11091.
36. L. Francis, A. Balakrishnan, K.P. Sanosh and E. Marsano, *Mater. Lett.*, 64 (2010) 1806.
37. L. Yan, L. Wei, R.B. Prakriti, *Macromol Biosci*., 77 (2006) 532.
38. H. Fong, I. Chun and D.H. Reneker, *Polymer*, 40 (1999) 4585.
39. S. Shukla, E. Brinley, H. J. Cho and S. Seal, *Polymer*, 46.26 (2005) 12130.