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Research Article

Formulation and Evaluation of Duloxetine Loaded Electro Spun Nanofibers for Extended Release

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Abstract

The aim of this work is to prepare Duloxetine nanofibers and evaluate the drug release profile by using PVA, Eudragit-S-100 and Eudragit L-100 55 polymers. Nanofibers were prepared by using conventional electrospinning technique. Duloxetine and polymers (PVA, Eudragit-S-100, Eudragit L-100 55) were used in ratio 1:1, 1:2, 1:4. The nanofibers were evaluated for its diameter by using SEM, the drug polymer interaction by using IR, then evaluated for drug release profiles of the nanofibers. The diameter of PVA, Eudragit-S-100 and Eudragit L-100 55 polymer nanofibers were in range of 150-200 nm. The dissolution profiles of Duloxetine loaded nanofibers were in order PVA (1:1)> EL (1:1)>PVA (1:4)>ES (1:1)>EL (1:4)>ES (1:2)>ES (1:4).

Keywords: Nanofibers, Electrospinning, Scanning Electron Microscope (SEM), Infrared Spectrophotometer (IR), Poly Vinyl Alochol (PVA), Eudragit-S-100, Eudragit L-100 55

Introduction

Nanofibers are defined as the fibers with diameter less than 1000 nm. Nanofibers are prepared by melt processing, interfacial polymerization, electrospinning, antisolvent-induced polymer precipitation and electrostatic spinning. Electrospinning is a widely used technique for the preparation of nanofibers. Electrospinning is a simple and versatile technique that utilizes electrostatic forces to produce very fine fibers of polymer ranging from submicron to nanometer sizes. The technique can be applied to generate fibers of a wide array of polymer types—synthetic [1], natural [2], biodegradable [3, 4], nonbiodegradable [5], or their blends [3,6]. The process of electrospinning has been derived from the established process of electrospraying that utilizes the same principle of applying an electric potential to a polymer liquid and causing a jet of liquid to accelerate from a capillary tip towards an oppositely charged collector [7]. When the liquid to which the potential is applied has a low viscosity, the jet, during its trajectory, will break up due to the surface tension resulting in the formation of polymer droplets instead of fibers [8, 9]. This is known as electrospraying. Apart from the surface tension and forces of the polymer solution, that is electrospun, there are various other processing variables that are deciding factors for the final outcome of the process and the performance of the fabricated nanofibers. Although the electrospinning process appears to be technically simple, a number of processing variables need to be regulated in order to generate nanofibers instead of droplets or beaded morphologies. The major challenge of the electrospinning process lies in the optimization of these parameters to achieve desirable nanofiber morphology and properties. The processing variables for electrospinning unit are applied voltage [10], solution flow-rate, polymer concentration, solution viscosity, nature of solvent, solution conductivity, distance between the capillary and collector.

Eudragits L and S, which are anionic copolymers of methacrylic acid and methyl methacrylate, have been widely used. These polymers are insoluble at low pH but form salts and dissolve above pH 6 and 7, respectively. The choice of the polymer depends on the pH of Duloxetine dissolution buffer (6.8).

The aim of the present work is to prepare Duloxetine embedded nanofibers using PVA, Eudragit-S-100 and Eudragit L-100 55 polymers for extended release, to study the drug release pattern of Duloxetine loaded nanofibers.

Duloxetine hydrochloride is an anti-depressant drug and a serotonin-nor epinephrine reuptake inhibitor. Duloxetine also has approval for use in osteoarthritis and musculoskeletal pain. It can also relieve the symptoms of painful peripheral neuropathy, particularly diabetic neuropathy and it is used to control the symptoms of fibromyalgia [11].

Materials and Methods

Materials

Duloxetine (Nosch Labs), Poly vinyl alcohol (PVA) (SD Fine, Mumbai), Eudragit-S- 100, Eudragit L-100 55 (Evonik), ethanol (SD Fine, Mumbai), acetone (Merck), potassium di hydrogen orthophosphate (KH_2PO_4) (SD Fine, Mumbai), hydrochloric acid (SD Fine, Mumbai) were obtained from above mentioned sources.

Calibration Curve of Duloxetine

Preparation of pH 6.8 KH_2PO_4 buffer [USP]:

50ml of 0.2M Potassium dihydrogen phosphate solution was added in 200ml volumetric flask, 22.4 ml of 0.2M NaOH solution was added, mixed and final volume was made up with distilled water.

Preparation of pH 1.2 HCl buffer [USP]:

50ml of 0.2M Potassium dihydrogen phosphate solution was added in 200ml volumetric flask, 85 ml of 0.2M HCl solution was added, mixed and final volume was made up with distilled water.

Preparation of Calibration Curve of Duloxetine in pH 6.8 phosphate buffer

100mg of Duloxetine was weighed and dissolved in 100ml of pH 6.8 phosphate buffer (Stock I). Aliquots of 1ml from stock I was transferred to 100ml volumetric flask and diluted with pH 6.8 phosphate buffer (Stock II). The Stock II solutions were further diluted to get 1, 2, 3,4,5,6 μg/ml. The absorbance of the above dilutions was measured on a spectrophotometer at 218.5 nm using buffer as the blank. The concentration of Duloxetine used and the corresponding absorbance is given in Table 1. The absorbance was plotted against concentration as shown in the Figure 1. This calibration curve was used in the estimation of Duloxetine in the present study.

Table 1: Calibration curve of Duloxetine

Conc. (µg/ml)	Abs. (218.5nm)
0	0
1	0.1649
2	0.332556
3	0.4705
4	0.6291
5	0.7803
6	0.939433

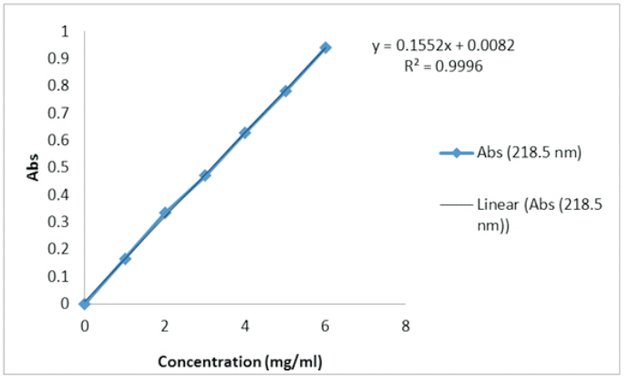

Figure 1: Calibraton curve

FTIR Spectroscopy Studies

The FTIR Spectra of the optimized batches of nanofibers of Duloxetine were studied to confirm the compatibility of the API with the excipients. FTIR spectroscopy was obtained by the FTIR spectrophotometer (Bruker) using the potassium bromide pellets and the scanning range used was 4400 to 400 cm^{-1} at a scan period of 1 min., reported in Figures 2, 3, 4, 5, 6, 7, 8 and Table 2.

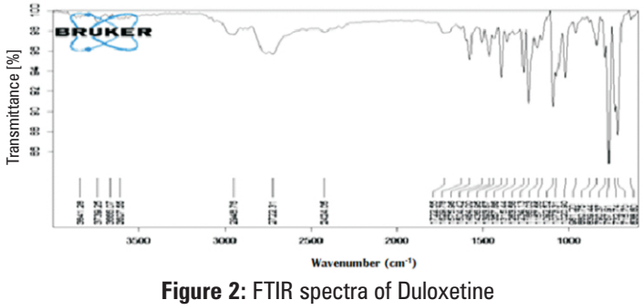

Figure 2: FTIR spectra of Duloxetine

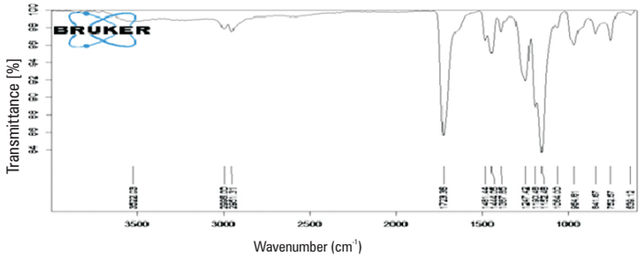

Figure 3: FTIR spectra of Eudragit-S-100

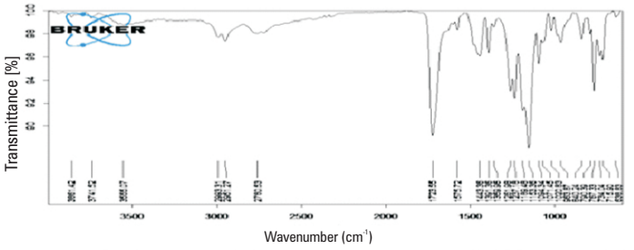

Figure 4: IR spectra of Duloxetine and Eudragit-S-100 in ratio 1:1

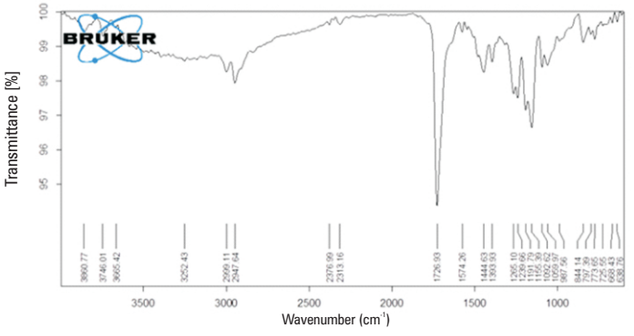

Figure 5: IR spectra of PVA

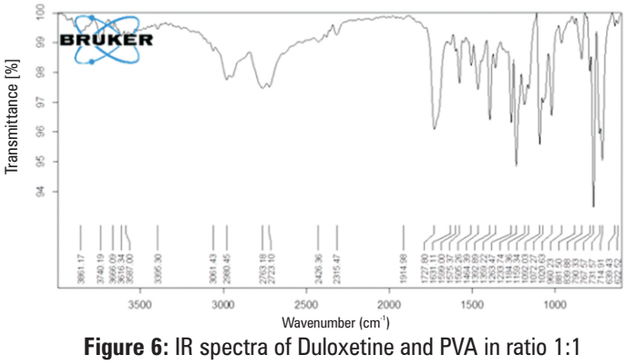

Figure 6: IR spectra of Duloxetine and PVA in ratio 1:1

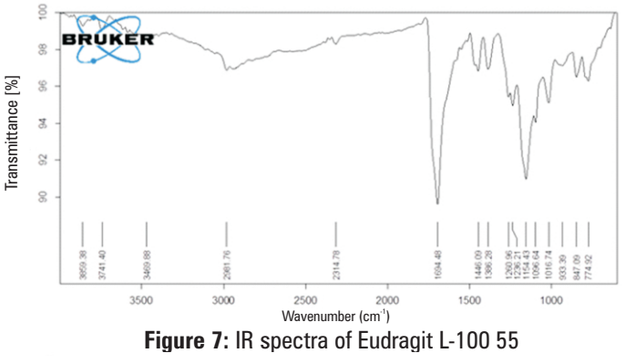

Figure 7: IR spectra of Eudragit L-100 55

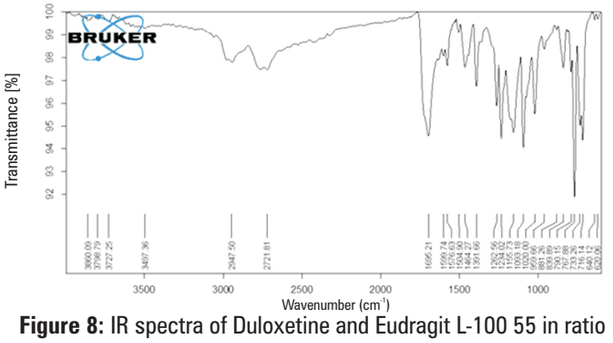

Figure 8: IR spectra of Duloxetine and Eudragit L-100 55 in ratio 1:1

Table 2: IR Spectral analysis of Nanofibers

S.No	Drug (cm-1)	Drug+PVA (cm^{-1})	Drug+Eudrtagit L-100 55(cm^{-1})	Drug+Eudragit-S 100(cm^{-1})
Aliphatic N-H stretch	3666.07	3616.43	3727.25	3741.52
C-O-C Stretch	1264.56	1263.47	1262.58	1261.98
C-S-C Stretch	1234.13	1233.74	1234.02	1237.18
Aromatic CH stretch	2948.76	2900.45	2947.50	2993.31

Preparation of Duloxetine Nanofibers

Preparation of Eudragit-S-100- Duloxetine nanofibers

Several trails were made using Eudragit-S-100 as a polymer. Various concentrations were prepared i.e., 25%, 20%, 17%, 15%, 13%, 10% (w/v). At 10% polymer solution it was found that fibers were formed. Increasing concentration leads to increase in viscosity thereby it would be difficult to pass through the syringe. Initially acetone was used as a solvent. We have found that acetone is more volatile, as the drop comes out from the syringe the solvent evaporates and polymer adhere to the needle tip causing flow problems. We have selected a co solvent in such a way that it should dissolve both the polymer and drug and should have high boiling point. We have taken ethanol water system in the ratio of 7:3. We have found that 25kv at which fibers were formed and at 10% of polymer concentration (Table 3).

Preparation of Eudragit L-100 55- Duloxetine nanofibers

Several trails were made using Eudragit L-100 55 as a polymer. At 11% (w/v) polymer solution, it was found that fibers were formed. We have selected a co solvent such a way that it should dissolve both the polymer and drug and should have high boiling point. We have taken ethanol water system in the ratio of 7:3. We have found that 25kv at which fibers were formed and at 11% of polymer concentration (Table 3).

Preparation of Duloxetine-PVA nanofibers

Several trials were done by preparing various concentration of polymer 7%, 8%, 9%, 10% in water. We have found that fibers were formed from the concentration range of 8-10%. The ideal voltage for formation of nanofibers was found to be 18kv. The flow rate was maintained at 0.3ml/hr (Table 3).

Table 3: Formula and Processing variables for preparation of Nanofibers

COMPOSITION	DULOXETIN:EUDRAGIT S 100	DULOXETIN:EUDRAGIT L 100	DULOXETIN:PVA
Batch code	ES1 ES2 ES3	EL1 EL2	PD1 PD2
Ratio	1:1 1:2 1:4	1:1 1:4	1:1 1:4
Voltage	25 KV	25 KV	18 KV
Flow rate	1mL	1mL	0.3 mL
Distance		12cm	
Syringe		2.5 mL/ 24 gauge needle	
Solvents	Ethanol : water(7:3)	Ethanol : water(7:3)	Water

Characterization of Electospinning Nanofibers

SEM Studies

The external surface morphology and diameter of the nanofibers were studied by using scanning electron microscopy (SEM). The nanofibers were observed under a scanning electron microscope. They were mounted directly on to the SEM sample stub using double sided sticking tape and coated with gold film (thickness 200 nm) under reduced pressure (0.0001 mm of Hg) (Figures 9,10,11).

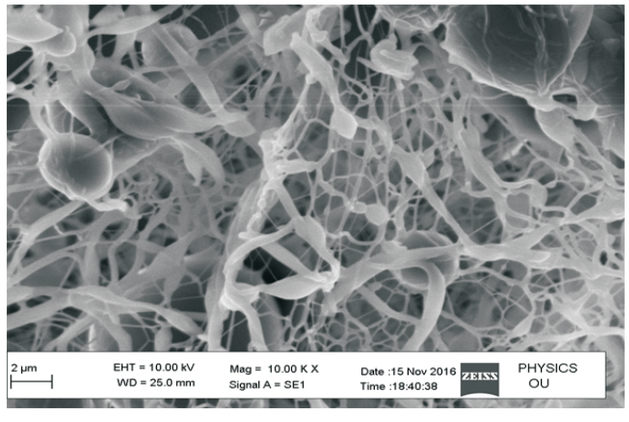

Figure 9: SEM image of Polyvinyl Alcohol nanofibers (1:1)

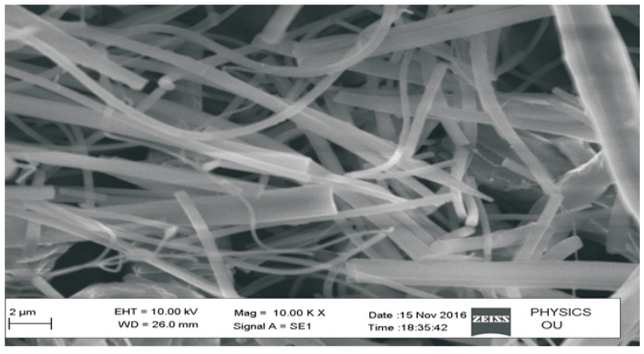

Figure 10: SEM image of Duloxetine Eudragit-S-100(1:1)

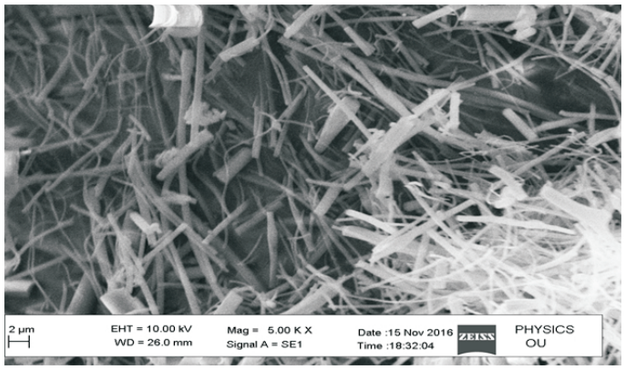

Figure 11: SEM image of Duloxetine- Eudragit L-100 55 (1:1)

In Vitro Dissolution Studies

Dissolution rate of Duloxetine from all the nanofibers was performed using dissolution testing apparatus with paddle. Initially the dissolution was carried out using pH 1.2 HCl bufferfor 2 hours and then pH 6.8 phosphate buffer for next 6 hours with 100rpm and 37.5ºC. The samples were collected 10, 20, 30, 45, 60 90, 120min first 2 hours and then for each hour for the next 6 hours (Table 4). The samples were analyzed using UV spectrophotometer at wavelength 218.5nm (Figures 12, 13).

Table 4: Drug Release of Duloxetine from Nanofibers

Time(min)	Cumulative % Drug Release						
	PVA 1:1	EL 1:1	PVA 1:4	EL 1:4	ES 1:1	ES 1:2	ES 1:4
10	2.7±0.01	0.21±0.01	4.98±0.21	1.40±0.23	0.55±0.11	0.82±0.09	0.58±0.09
20	2.75±0.01	0.40±0.02	5.85±0.17	2.01±0.41	3.26±0.07	1.58±0.08	0.76±0.05
30	2.96±0.01	1.47±0.32	6.08±0.08	2.64±0.15	3.38±0.03	3.15±0.08	0.90±0.02
45	3.11±0.03	1.57±0.12	6.43±0.15	4.33±0.29	3.60±0.07	4.5±0.21	2.50±0.02
60	3.29±0.09	2.36±0.25	7.06±0.09	6.51±0.03	3.84±0.08	6.95±0.23	2.72±0.19
90	4.10±0.02	3.63±0.75	8.06±0.13	7.01±0.17	4.27±0.12	8.60±0.31	5.59±0.14
120	5.05±0.16	4.49±0.66	8.81±0.03	7.62±0.14	5.81±0.15	9.83±0.57	8.30±0.09
180	51.01±0.16	24.24±2.14	23.20±0.08	36.55±1.27	43.66±0.71	28.26±1.49	10.72±0.56
240	57.92±0.05	31.14±1.44	40.98±0.52	45.84±0.67	48.10±0.77	37.64±1.43	32±0.18
300	65.34±0.06	40.38±1.20	52.15±1.65	55.72±0.85	70.70±0.28	38.28±1.47	33.88±0.53
360	71.45±0.29	51.20±2.90	55.05±1.67	61.38±0.21	73.16±0.67	39.75±0.81	34.11±0.17
420	87.17±0.09	61.11±1.36	80.92±0.44	68.76±0.61	80.70±0.76	42.32±0.50	37.42±0.61
480	98.020.14	95.12±0.29	91.93±0.99	75.31±0.45	82.35±0.20	51.99±0.53	41.58±0.78

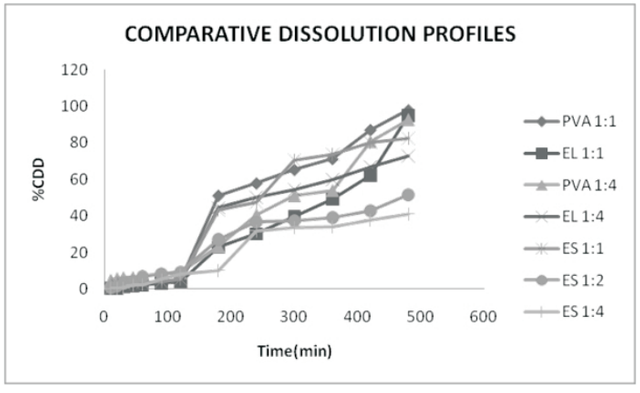

Figure 12: Comparative Dissolution profiles

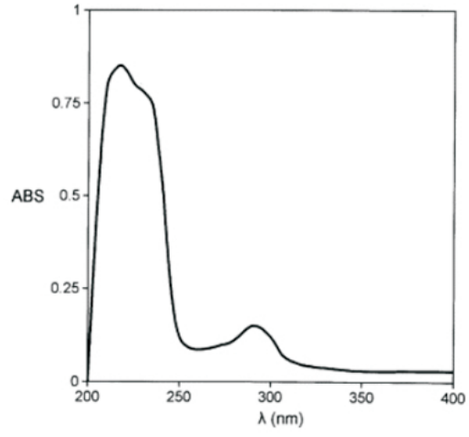

Figure 13: UV spectra of Duloxetine

Results and Discussion

In the present study Duloxetine embedded extended release nanofibers, using polymers PVA, Eudragit-S-100, Eudragit L-100 55 as matrix material were prepared. PVA nanofibers were formed at 10% concentration of polymer, 0.3 ml/hr flow rate and 18 kV voltage. Eudragit-S-100 nanofibers were formed at 10% concentration of polymer, 1 ml/hr flow rate and 25 kV voltage. Eudragit L-100 55 nanofibers were formed at 11% concentration of polymer, 1 ml/hr flow rate and 25 kV voltage. SEM photo-micrographs of PVA-Duloxetine nanofibers (10000X) revealed bead formation in the nanofibers (size range 150-200 nm). SEM photo-micrographs of Eudragit- S-100-Duloxetine nanofibers (10000X) revealed formation of nanofibers without beads with smooth surface texture (size range 150-200 nm). SEM photo-micrographs of Eudragit L-100 55-Duloxetine nanofibers (5000X) revealed formation of brittle nanofibers without beads with smooth surface texture (size range 150-200 nm). Since all the characteristic IR peaks of the pure drug are found in all IR spectra of the formulations, there are no drug-polymer interactions. From in-vitro drug release studies, the drug release rate was found to be: PVA (1:1)> EL (1:1)> PVA (1:4)>ES (1:1)>EL (1:4)>ES (1:2)>ES (1:4). PVA (1:1) nanofibers have shown 98% drug release in 8 hours with burst release (46% in 1 hour) whereas EL (1:1) nanofibers have shown sustained drug release with 95% drug release in 8 hours and ES (1:1) nanofibers also displayed sustained release with only 82% drug release in the same period. Drug release from all the formulations in acid medium (pH 1.2 HCl buffer) in first two hours was found to be less than 10%. At the end of the third hour PVA (1:1) shows highest drug release of 51% among all the formulation and ES (1:4) the least drug release 10.72%. At the end of the 8th hour, the cumulative percentage drug release from the formulations was found to be in the range of 41.58 (ES 1:4) to 98% (PVA 1:1). Based on the cumulative percent drug release at the end of the 8th hour formulation ES (1:1) can be considered as optimized formulation which releases more than 82% Duloxetine and complete drug release may be expected in another 2 hours. Drug: polymer in 1:1 ratios has shown a greater release when compared to the ratio 1:4. ES 1:1 ratio has shown greater release when compared to ES (1:2), ES (1:4).

Conclusion

From the present work we have concluded that the polymers like Eudragit-S-100 and Eudragit L- 100 55 can form nanofibers for extended release of Duloxetine. Selection of solvent, viscosity, and ratios of drug: Polymers were important for successful preparation of electrospun nanofibers. Optimized formulation method was selected. Based on the SEM images, the fiber diameters were in 150-200nm range; among the polymers used Eudragit-S-100 (1:1) gives nanofibers with smooth texture. The optimized formulation (ES 1:1) prepared with Eudragit-S-100 was found to be promising with good sustained release effect without any burst release.

Conflict of interest

The authors declare no conflict of interest.

References

[1]. Ma Z, Kotaki M, Yong T, He W, Ramakrishna S. Surface engineering of electrospun polyethylene terephthalate (PET) nanofibers towards development of a new material for blood vessel engineering: Biomater 2005; 26(15):2527-36.

[2]. Chen JP, Chang GY, Chen JK. Electrospun collagen/chitosan nanofibrous membrane as wound dressing: Colloids and Surfaces A: Physicochemical and Engineering Aspects 2008; 313:183-8.

[3]. Kim TG, Lee DS, Park TG. Controlled protein release from electrospun biodegradable fiber mesh composed of poly (**ε**-caprolactone) and poly (ethylene oxide): Int J Pharmaceutics 2007; 338(1):276-83.

[4]. Maretschek S, Greiner A, Kissel T. Electrospun biodegradable nanofiber nonwovens for controlled release of proteins: J controlled Release 2008; 127(2):180-7.

[5]. Verreck G, Chun I, Rosenblatt J, Peeters J, Van Dijck A, Mensch J, Noppe M, Brewster ME. Incorporation of drugs in an amorphous state into electrospun nanofibers composed of a water-insoluble, nonbiodegradable polymer: J Controlled Release 2003; 92(3):349-60.

[6]. Deng XL, Sui G, Zhao ML, Chen GQ, Yang XP. Poly (L-lactic acid)/hydroxyapatite hybrid nanofibrous scaffolds prepared by electrospinning: J Biomat Sci, Polymer Edition 2007; 18(1):117-30.

[7]. Taylor G. Electrically driven jets: In Proceedings of the Royal Society of London A Mathematical, Physical and Engineering Sciences 1969, 313(1515):453-75.

[8]. Deitzel JM, Kleinmeyer J, Harris DE, Tan NB. The effect of processing variables on the morphology of electrospunnanofibers and textiles: Polymer 2001; 42(1):261-72.

[9]. Hogan CJ, Biswas P. Narrow size distribution nanoparticle production by electrospray processing of ferritin: J Aerosol Sci 2008; 39(5):432-40.

[10]. Bhardwaj N, Kundu SC. Electrospinning: a fascinating fiber fabrication technique: Biotech adv 2010; 28(3):325-47.

[11]. Kuang, C, Sun Y, Li B, Fan R, Zhang J, Yao Y, He Z. Preparation and evaluation of Duloxetine hydrochloride enteric-coated pellets with different enteric polymers: Asian J pharm sci 2017; 12(3):216-26.