İstanbul Journal of Pharmacy,
IJP 2025, 55 (3): 318–331

https://doi.org/10.26650/IstanbulJPharm.2025.1635537
Submitted: 07.02.2025
Revision Requested: 07.04.2025
Last Revision Received: 10.06.2025
Accepted: 29.08.2025

İstanbul Journal of Pharmacy

Research Article

Open Access

Preparation and *in vitro* Characterisation of Nanofibers for Enhancing the Water Solubility of Poorly Soluble Drugs

Elif Karamürsel [1], Egemen Uzel [2], Neriman Aydilek [1], Meltem Ezgi Durgun [3] & Yıldız Özsoy [1]

[1] İstanbul University, Faculty of Pharmacy, Department of Pharmaceutical Technology, İstanbul, Türkiye
[2] İstanbul Yeni Yüzyıl University, Faculty of Pharmacy, Department of Pharmaceutical Technology, İstanbul, Türkiye
[3] İstanbul Health and Technology University, Faculty of Pharmacy, Department of Pharmaceutical Technology, İstanbul, Türkiye

Abstract

Background and Aims: As the drug discoveries of the modern century have led to a rapid increase in the number of new drug candidates with low water solubility, nanofiber drug delivery systems have become a promising technology to increase the water solubility of drugs with a high surface-to-volume ratio. In this study, we aimed to prepare a nanofiber of a molecule with low water solubility and investigate its changing solubility properties.

Methods: Three nanofiber dosage forms containing olanzapine (OLZ) active substance were developed by the electrospinning method using polyvinyl alcohol (PVA) polymer. Drug loading efficiency, zeta potential determination, electrical conductivity, rheology, field emission scanning electron microscopy (FESEM), Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and X-ray diffraction (XRD) analyses were performed to evaluate the *in vitro* characterisation of the formulations. The solubility profile of the optimised formulations in pH 7.4 phosphate buffer was evaluated. The stability of optimised formulations was evaluated in terms of physical properties (colour, shape, weight, diameter, and thickness) and drug amount for 35 days.

Results: It was determined that the electrospinning property of the nanofiber preparation solution increased with the addition of ethanol to the polymer solvent medium. The active substance distribution in the nanofiber layer was more homogeneous in the N78 and N79 coded formulations with high zeta potential values compared to N69. Contrary to the homogeneous distribution problem, the loading efficiency of the N69-coded formulation containing chloroform (~29%) was higher than that of N79 (~9.8%). A 24-h solubility study in pH 7.4 phosphate buffer of the N78-coded formulation, which has an active ingredient loading efficiency of ~80.4%, confirmed the increased solubility of OLZ in water in the nanofiber drug delivery system.

Conclusion: Further studies are needed to convert these model formulations into final drug products.

Keywords Bioavailability · Nanofibers · Olanzapine · Solubility

Citation: Karamürsel, E., Uzel, E., Aydilek, N., Durgun, M. E. & Özsoy, Y. (2025). Preparation and *in vitro* characterisation of nanofibers for enhancing the water solubility of poorly soluble drugs. *İstanbul Journal of Pharmacy*, *55*(3), 318-331. https://doi.org/10.26650/IstanbulJPharm.2025.1635537

Corresponding author: Elif Karamürsel elifkaramursel@gmail.com

INTRODUCTION

In the modern century of drug discovery, some drug development methods, such as high-throughput screening, combinatorial chemistry, and receptor binding by hydrophobic interaction, used to increase the yield and potency, have led to the increase of new drug candidates with poor water solubility (Khan et al., 2022; Marano et al., 2016). Poor water solubility is the main reason why many drug candidates fail in clinical trials despite showing good therapeutic activity in animal studies (Das et al., 2022). Various molecule- or therapy-based alternatives can be developed to overcome the problems of poor absorption and low bioavailability of poorly soluble compounds. However, these solutions may result in increased cost and time in production, impaired treatment compliance, and toxicity (Savjani et al., 2012). The most widely used strategies to improve solubility in the pharmaceutical industry are particle size reduction (nano-sizing), the use of amorphous forms, and lipid-based drug delivery systems. All these approaches are embodied by the availability of various products on the market (Löbmann & Svagan, 2017).

Olanzapine (OLZ), which has high clinical value as an antipsychotic agent, is a poorly water-soluble molecule that hardly crosses the blood-brain barrier. It undergoes hepatic first-pass metabolism before reaching the systemic circulation (57% oral bioavailability). Increasing the starting dose to increase bioavailability in the brain may be considered, but the severity of the side effects should be assessed (Haddad et al., 2014; Meftah et al., 2020; Natarajan et al., 2017). Orally disintegrating tablets and intramuscular injections have been developed to overcome the bioavailability issues of OLZ; however, these have been found to have similar bioavailability to conventional tablets (Khallaf et al., 2020). Solid lipid nanoparticles of OLZ increased bioavailability up to 23-fold, but their perfect crystalline structure reduced the drug loading capacity (Ghasemiyeh & Mohammadi-Samani, 2018; Zorkina et al., 2020). Although the nanostructured lipid carriers of OLZ, which are directly targeted to the brain by intranasal administration, increased bioavailability, the possible cytotoxic effect of lipids was limiting (Chauhan et al., 2020). Niosomes with a particle size of 250 nm enabled the controlled extended release of OLZ (Singh et al., 2018). However, the chemical stability problem of phospholipids required the formulation to be kept under special storage conditions (Ferreira et al., 2023).

Nanofibers, an attractive technology in nano-sizing, are structures with high specific surface area and surface area/volume ratio (10,000 - 1,000,000,000 m^2/kg), with diameters ranging from 5 to 500 nm, in diameter which can form highly porous networks (Barhoum et al., 2019; Pattnaik et al., 2023). In particular, polymer nanofibers are an advantageous drug delivery system because of their biocompatibility, high stability, and similarity to the extracellular matrix (Kajdič et al., 2020; Vuddanda et al., 2016). Continuous and mass production of nanofibers can be achieved by the electrospinning method, which is a simple and cost-effective method (Barhoum et al., 2019). During electrospinning, which is an electrostatic fibre production process, the solvent in the polymer solution evaporates rapidly, and nanofibers are formed instantly, while the drug is trapped in the polymer matrix or deposited on the nanofiber surface. Drug mobility is reduced. It is usually randomly encapsulated in the nanofiber (Martínez-Pérez, 2020; Pattnaik et al., 2023; Potrč et al., 2015).

The size of the nanofibers depends on the process parameters such as the solution, media and polymer concentration, electric field and flow rate of the feed solution. Fibres with a diameter of 10-1000 nm and a smooth surface morphology are mostly preferred (Al-Hazeem, 2018; Gugulothu et al., 2019). Nanofibers with the desired properties can be produced with appropriate polymer selection (Gugulothu et al., 2019; Zahmatkeshan et al., 2019). Poly (vinyl alcohol) (PVA), whose aqueous solution can be easily prepared and electrospun, is a preferred polymer for nanofiber preparation to increase water solubility. Biodegradable, biocompatible and semi-crystalline, PVA stands out with its chemically stable structure under normal temperature and good physical and mechanical properties (Acik, 2020; C. Zhang et al., 2005).

In this study, we aimed to develop nanofibers of OLZ by the electrospinning method using a suitable polymer solution determined to increase its water solubility. Nanofibers of OLZ with PVA were developed and *in vitro* characterisation of the selected final formulations was evaluated.

MATERIALS AND METHODS

Materials

OLZ was kindly gifted by Genveon Pharmaceutical Company (Turkey), sourced from India. The PVA-polyethylene glycol graft co-polymer (Kollicoat® Protect) was purchased from BASF (Germany). Methanol (high-pressure liquid chromatography-HPLC grade) and acetonitrile (HPLC grade) were purchased from Merck (Germany). Ethanol and tert-butanol were of analytical grade and were purchased from Merck (Germany). Dichloromethane, hydroxypropyl methylcellulose (HPMC) (60 M), chloroform, and trifluoroacetic acid were purchased from Merck (Germany). Dimethyl sulfoxide (DMSO) was obtained from Sigma-Aldrich (Massachusetts, USA). The ultrapure water was supplied by the Millipore Milli-Q ultrapure water system (Massachusetts, USA).

Methods

Preparation of Solutions for the Electrospinning Process

For the electrospinning process, the solutions of HPMC and PVA were prepared under magnetic stirring at 600 rpm – 50 °C and 800 rpm – 100 °C for 3 h each, respectively. For the OLZ-loaded nanofiber solutions, 10 mg/mL OLZ was dissolved in 5 mL dichloromethane and 5 mL chloroform at room temperature and combined with the polymer solution in a 3:1 (v/v) ratio (Meftah et al., 2020).

All solutions were degassed in an ultrasonic bath at room temperature for 15 min before electrospinning. Then, the solutions were taken into 10 mL injections and kept upright in the injection for 30 min.

Electrospinning

All electrospinning processes were performed using a 35-40 cm long polycarbonate column and a 10-mL syringe. The nanofibers were collected on aluminium foil and greaseproof paper fixed on the collector. A cylinder collector and a flat collector were used, and a nozzle and 19 G and 21 G needle tips were used as the exit tip of the nanofiber solution.

HPLC Analysis of the OLZ

OLZ quantification was performed using a modified HPLC method by replacing the diluent medium with methanol (Albayrak, 2014). A C18 (Inertsil ODS-3 5 micrometre 4.6 x 260 mm) column and UV detector were used. The column temperature was set to 25 °C and the flow rate to 1 mL/min. The injection volume was 10 µl and the mobile phase was methanol:acetonitrile:water (containing 0.1% TFA) (40:30:30, v/v/v). The retention peak of OLZ at 272 nm was observed at 2.10 min. This validated method was used to determine the OLZ content in each nanofiber formulation.

In vitro Characterisation of the Solutions for Electrospinning

Measurements were made on a single nanofiber preparation solution for formulations coded N78 and N79, which differed from each other only by the electrospinning parameters.

Measurement of the Zeta Potential

The zeta potentials of the solutions for electrospinning were determined by the electrophoretic light scattering method using 3 measurements with 12 replicates each. The Zetasizer NanoZS (Malvern, UK) instrument was used with an accuracy of ± 0.1 °C at 25 °C using a convoluted capillary cuvette.

Measurement of the Electrical Conductivity

The electrical conductivity of the 20 mL nanofiber preparation solutions was measured at room temperature with an Eutech Instruments, PC2700 (Landsmeer, The Netherlands).

Rheological Studies

The bulk and interfacial rheological properties of the nanofiber preparation solutions were measured in triplicate with HAAKE RheoStress 1 (Thermo Scientific, Germany) at 25 °C in the shear rate range of 0-360 s^{-1}, using a parallel plate sensor (gap = 0.5 mm) in triplicate. Evaluations were performed according to the exponential law equation using HAAKE RheoWin 3 Data manager software (Thermo Scientific, Germany) (Rošic et al., 2013).

In Vitro Characterisations of Nanofibers

FESEM Imaging

For FESEM imaging, 6 mm x 6 mm samples were coated with a thin layer of gold using a sputter coater for 60 s (Apreo 2S (Thermo Scientific, Germany)). The average diameter of the nanofibers was calculated at 50 different points of the images with ImageJ software (LOCI, University of Wisconsin, Wisconsin, US) (Vashisth et al., 2014).

DSC Analysis

DSC analysis (DSC 3500 Sirius (Netzsch, Germany)) was performed under a nitrogen gas atmosphere with three repetitions per sample. Each sample was weighed and placed in aluminium containers and heated to 25°C to 600 °C at a heating rate of 10 °C/min (Koosha & Mirzadeh, 2015).

XRD Mapping

XRD mapping of the nanofibers was performed using X'Pert PRO (Malvern Panalytical, UK). The electrospun nanofibers were analysed by a wide-angle X-ray diffractometer using a CuKα radiation source with a wavelength of λ=0.154 nm operating at 40 kV and 30 mA. The intensity was recorded in the range from 5º to 118º, with a step size of 0.032º (Koosha & Mirzadeh, 2015).

FTIR Analysis

Material analysis at the molecular level was performed by FTIR measurement with Spectrum™ 100 (Perkin Elmer, Waltham, US). The film samples were cut into small pieces, and a pinch of the nanofiber sample was filled into the sample trough plate before analysis, and the IR spectra were recorded

under reduced vacuum. The scan and resolution range were 650-4000 cm^{-1} and 2 cm^{-1}, respectively (Vuddanda et al., 2016).

Yield and Encapsulation Efficiency

The 6 mm x 6 mm samples were placed in tubes containing 2 mL methanol for 45 min and centrifuged at 5000 rpm for 15 min. 1 mL of the samples was taken and the amount of OLZ was determined by the HPLC method described. The yield and encapsulation efficiency of the nanofibers were calculated using the following formulas (Józó et al., 2021):

$$Yield\ (\%) = \frac{Actual\ amount\ of\ OLZ\ (\mu g)}{Theoretical\ amount\ of\ OLZ\ (mg)} x100 \quad (1)$$

$$Encapsulation\ efficiency\ (\%) = \frac{Actual\ amount\ of\ OLZ(\mu g)}{Theoretical\ amount\ of\ OLZ\ (mg) + Theoretical\ amount\ of\ polymer\ (g)} x100 \quad (2)$$

In vitro Solubility Study

OLZ and the selected formulations were taken into tubes and 2 mL phosphate buffer was added to each, more than the maximum amount that should be dissolved. The samples in the tubes were shaken on an orbital shaker at 300 rpm for 24 h at room temperature. Insoluble OLZ was precipitated by centrifugation at 15000 rpm for 15 min. The samples were filtered through a 0.45 µm nylon filter, diluted 1:9 (v/v) with methanol, and transferred to vials, and OLZ was quantified by the HPLC method as described. Each sample was analysed in triplicate.

Stability Studies

The stability tests of the selected formulations were conducted in aluminium packaging under conditions of "25 ± 2 °C, 60 ± 5% relative humidity" and "40 ± 2 °C, 75 ± 5% relative humidity" in stability chambers (Yosef Kinani et al., 2022). The samples were evaluated on days 7, 14, 21, 28, and 35 in terms of physical characteristics (colour and shape, by visual inspection), weight (using a precision balance), and diameter-thickness (using a calliper). OLZ was quantified by the HPLC method as described.

Statistical Analysis

The findings of the experiment were statistically analysed using GraphPad Prism 8.1.1 (GraphPad Software, Boston, USA) software. The "one-way ANOVA test" was applied when there were more than two comparison items, and the "t-test" was applied when there were two comparison items. Since the stability results were examined according to multiple time points, the statistical analysis of the stability studies was performed according to linear regression.

RESULTS AND DISCUSSION

Pre-formulation Studies

In the first stage of the pre-formulation studies, it was aimed to determine the appropriate polymer solution that can be electrospun with reproducible parameters and can form smooth nanofiber layers with continuous production. To increase the water solubility, solutions were prepared with the selected PVA and HPMC polymers at the concentrations specified in Table 1.

Table 1. Polymers and concentrations used in the determination of the appropriate polymer solution and maximum values applied in the electrospinning trials

Polymer	Concentration (%, w/w)	Maximum voltage applied (kV)	Maximum flow applied (mL/h)
HPMC	1	25	2.5
	2	28	2.5
	3	28	2.5
	4	29	2.5
	5	30	2.5
	8	6	0.5
PVA*	15	10	1
	18	15	1
	20	32	10
	30	25	5
	40	27	5
PVA**	20	23	3
HPMC:PVA**	0.5:20	27	1
	0.7:20	27	1
	1:20	30	1

* Solution of PVA in water; **Solution of PVA in water and ethanol. PVA: polyvinyl alcohol; HPMC: hydroxypropyl methylcellulose.

Electrospinning with low-concentration HPMC solutions showed electrospray-like results, where the solution accumulated in small droplets in the collector before the nanofibers were formed. In the case of HPMC solutions with concentrations of 2% and above, the deposition of the polymer solution at the outlet end could not be avoided despite the use of the nozzle with the largest inner diameter and increasing the voltage and flow throughout the electrospinning process. This concentration-dependent behaviour of HPMC can be explained by the fact that the polymer chain linkage in solutions that do not reach the critical viscosity cannot overcome the colonic repulsion, forming droplets instead of continuous fibres. The "spraying" of the solution and the formation of

beads agrees with the low concentration. In the opposite case, the solution is expected to accumulate at the exit end (Fatahian et al., 2021; Garcia et al., 2022; Paaver et al., 2015, 2019; Verreck et al., 2003).

Pre-formulation studies with PVA-based solutions were quite good compared to the results obtained using HPMC. Nanofiber formation was observed macroscopically in all formulations indicated in Table 1. This superiority of PVA over HPMC in electrospinning can be explained by the slower evaporation of PVA (Ojha, 2007). Production with 20% aqueous solutions of PVA showed more stable and reproducible parameters. This led to further research to improve the continuity of production. Ethanol was added to the solvent medium of the polymer to improve the electrospinnability and nanofiber quality (Figure 1) (Józó et al., 2021; Ramakrishnan et al., 2019; Rošic et al., 2013).

Nanofiber production with the PVA:water:ethanol (20:40:40, w/w/w) polymer solution was carried out with the parameters indicated in Table 2. Stable and reproducible results were obtained from the formulations using greaseproof paper on a flat collector as the collector and a nozzle as the exit end.

Based on the good results of PVA in nanofiber production (Figure 1), nanofiber production with the PVA-HPMC solution was investigated. No fibre formation and electrospraying were observed in the experiments with the concentrations and parameters in Table 1. With this result, formulation development studies were continued with solutions using only PVA.

In the second stage of the pre-formulation studies, the organic solvent suitable for the preparation of the solution of OLZ and PVA and compatible with electrospinnability was investigated. The formulations containing DMSO and tert-butanol became heterogeneous in a short time. The rheological properties of the PVA solutions can vary with the affinity of the different components in the solution for each other. DMSO and water show a high affinity for each other. This can cause the liquid-liquid mixture to have polymer-rich and poor phases, as the viscosity (bulk and interfacial) and relaxation time will change (Gupta et al., 2016). Continuous and reproducible nanofibers were produced under 19 kV with solutions using dichloromethane and chloroform as organic solvents.

Optimisation of the Nanofiber Formulations

To determine the appropriate electrospinning process parameters for continuous nanofiber production, over 40 formulations containing active ingredients were developed. The optimised process parameters of the formulations that yielded smooth nanofibers on macroscopic examination, no beads were detected on microscopic examination, and the production was reproducible and continuous are given in Table 3. These parameters are in agreement with the studies in the literature where successful nanofiber production with PVA has been realised (Fathollahipour et al., 2015; Mata et al., 2022).

Consistent with the literature, bead formation was observed to increase with increasing flow rate and voltage, i.e., the electric field (Figure 1 and Figure 2) (Bhardwaj & Kundu, 2010; C. Zhang et al., 2005). As the distance between the collector and the needle tip decreased, thicker fibres were detected, and as the distance increased, thin and curly fibres were detected. As the distance increases, the scattering area of the fibres deposited in the collector increases, which can cause the fibres to become thinner (Sill & von Recum, 2008;

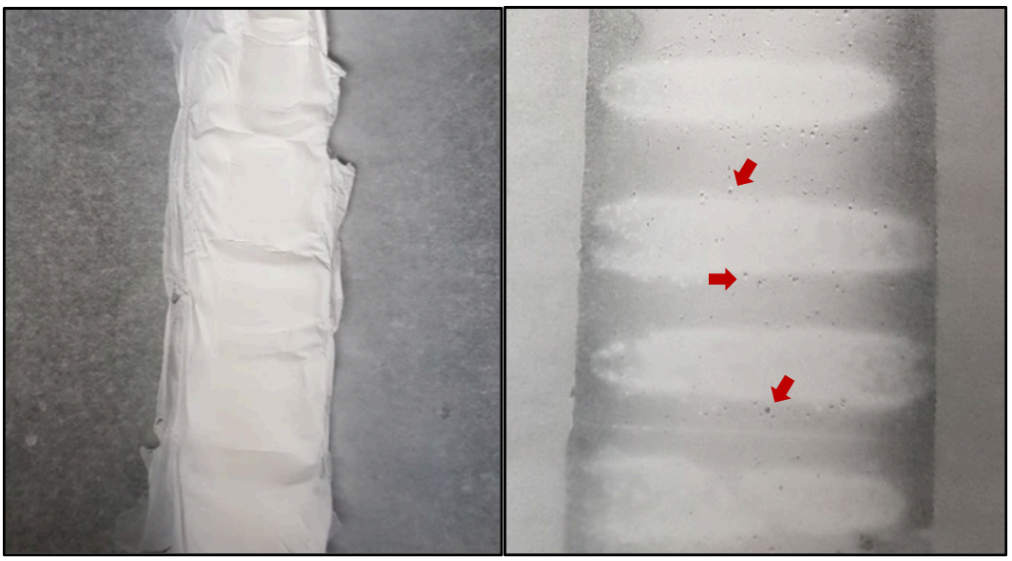

Figure 1. The smooth nanofiber layer was collected on greaseproof paper in a flat collector with PVA:water:ethanol (20:40:40, w/w/w) solution and the beaded nanofiber structure was obtained from the 20% PVA solution under high voltage and flow. (PVA: Polyvinyl alcohol; HPMC: Hydroxypropyl methylcellulose)

Table 2. Optimised electrospinning process parameters and results for the PVA:water:ethanol (20:40:40, w/w/w) solution

Formulation	Collector type	Output type	Voltage (kV)	Flow (mL/h)	Distance (mm)	Bead-free fibre on microscopic examination
N19	Flat	Nozul	13	1	50	Yes
N20	Flat	Nozul	17	2	80	Yes
N21	Flat	Nozul	23	3	120	Yes
N27	Flat	19G	7	1	50	Yes
N28	Flat	21G	6	1	50	Yes
N45	Cylinder	21G	10	2	70	No
N46	Flat	21G	10	2	90	No
N47	Flat	21G	9	2	90	No
N48	Flat	Nozul	16	0.7	120	No
N49	Flat	Nozul	18	0.7	150	No
N50	Flat	Nozul	19	0.7	180	No
N51	Flat	Nozul	16	0.8	120	No
N52	Flat	Nozul	18	0.8	150	No
N53	Flat	Nozul	20	0.8	180	No
N54	Flat	Nozul	16	1	120	No
N55	Flat	Nozul	18	1	150	No
N56	Flat	Nozul	18	1	180	No

Table 3. Optimised electrospinning process parameters for formulations containing the active substance

Formulation	Organic solvent of the active ingredient	Voltage (kV)	Flow (mL/h)	Distance (mm)	Results		
					Macroscopic examination	Production	Microscopic examination
					Smooth nanofiber layer	Continuous and repeatable	Bead-free fibre image
N69	TCM	20	0.5	180	Yes	Yes	Yes
N78	DCM	18	0.5	120	Yes	Yes	Yes
N79	DCM	23	0.6	180	Yes	Yes	Yes

TCM: chloroform; DCM: dichloromethane

Zahmatkeshan et al., 2019). Production with a small-diameter needle tip also resulted in thin nanofibers (Figure 2) (He et al., 2019).

During fabrication, it was observed that the parameters of the electrospinning process were influenced by the type of collector and the material coated on the collector. Although

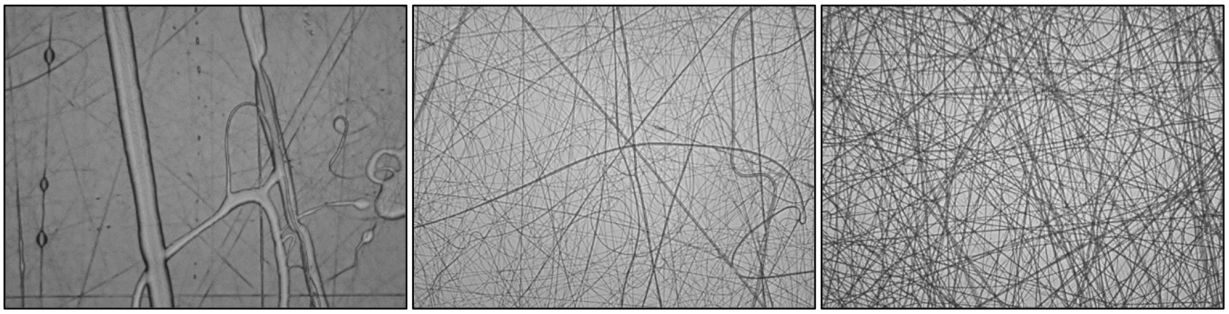

Figure 2. Microscope image of the nanofibers (from left to right: N91 coded dichloromethane-containing formulation (process parameters: 26 kV, 4 mL/h, 120 mm, nozzle tip); N96 coded chloroform-containing formulation (process parameters: 11 kV, 0.1 mL/h, 120 mm, 19G tip); N77 coded dichloromethane-containing formulation (process parameters: 15 kV, 0.1 mL/h, 80 mm, nozzle tip)).

the same formulation solution was used, different voltages were used for each pulse on the greaseproof paper, aluminium and glass lamellae. The reason for this difference may be the effect of the conductivity of the material wrapped on the collector on the electric field (Cardenas Bates et al., 2020) with the same formulation solution, it was observed that the productions in the cylinder collector were carried out at lower voltages compared to the production in the flat collector. This difference is explained by the fact that the polymer chains are subjected to tensile stress between the electrodes due to the increased solvent evaporation rate and simultaneously crystallise via "shear diffusion" to form long-chain β-crystals (Ojha, 2007). This process parameter, which changes the mechanical properties of the nanofibers, is thought to indirectly affect other parameters that must remain in equilibrium. In this study, production using a flat collector gave more stable and reproducible results.

In vitro Characterisation of Solutions

Measurements were made on a single nanofiber preparation solution for formulations coded N78 and N79, which differ only from each other by the electrospinning process parameters, and the results are represented with code N78 in Table 4.

Measurement of the Zeta Potential

The zeta potential was measured to determine the distribution uniformity and electrical stability of the solutions and the homogeneity of the nanofiber to be formed. It is known that zeta potentials lower than –25 mV or higher than +25 mV indicate good electrical stability for a given colloidal suspension (Naseri et al., 2015). The solutions showed negative zeta potential values, and the highest zeta potential value was determined in the solutions of formulations coded N78 and N79 containing dichloromethane. The decreasing dispersion stability with decreasing zeta potential value was evident as the solutions containing dichloromethane with higher zeta potential values gave more stable and reproducible results during electrospinning, showed higher electrical conductivity (Table 4) and more homogeneous dispersion of the active substance in the nanofiber layer (Table 5) (Chen et al., 2017; Fatahian et al., 2021; Pelipenko et al., 2015). It was concluded that these solutions containing dichloromethane are electrically more stable for electrospinning.

Measurement of the Electrical Conductivity

The electrical conductivity results are given in Table 4.

Table 4. Zeta potential (ZP) and electrical conductivity values (Σ) and rheological properties of the electrospinning solutions of the formulations (with and without the active ingredients) (n = 3)

Sample	ZP (Mv) (average ± SD)	Σ (μS) ± SD	Herschel-Bulkley				
			τ_0	K (Pa.sn)	n	Chi²	r
N69PS	–1.69 ± 0.15	160.26 ± 3.52	0 ± 1.02	0.53 ± 0.13	1.08 ± 1.00	1637.43 ± 2305.01	0.99 ± 0.00
N78PS	–1.98 ± 0.13	181.06 ± 7.92	4 ± 2.163	0.80 ± 0.06	0.96 ± 0.01	1427.96 ± 1394.95	0.99 ± 0.00
N69S	–1.67 ± 0.41	176.4 ± 4.16	–1 ± 0.45	0.57 ± 0.02	0.99 ± 0.00	502.2 ± 81.51	0.99 ± 1.35
N78S	–5.58 ± 0.53	203.6 ± 10.18	2 ± 1.39	0.49 ± 0.07	1.0 ± 0.02	543.03 ± 115.14	0.99 ± 5.77

N69PS: Placebo form of formulation solution of N69; N78PS: Placebo form of formulation solution of N78; N69S: Formulation solution of N69; N78S: Formulation solution of N78

Table 5. The amount of OLZ in the nanofibers and the loading efficiency according to its position in the nanofiber layer (n = 3)

Formulation	The region where the sample was taken	Amount of active substance in nanofiber (μg/mg) (average ± SD)	Nanofiber-loaded active ingredient (%, w/w) (average ± SD)
N69	Outer	0.423 ± 0.15	14.104 ± 5.10
	Middle	0.433 ± 0.10	14.464 ± 3.50
	Centre	0.8714 ± 0.24	29.0484 ± 8.32
N78	Outer	0.143 ± 0.07	4.79 ± 0.54
	Middle	0.689 ± 0.89	22.99 ± 0.70
	Centre	2.413 ± 0.19	80.4335 ± 0.88
N79	Outer	0.05 ± 0.02	1.68 ± 2.57
	Middle	0.099 ± 0.02	3.307 ± 1.88
	Centre	0.2955 ± 0.02	9.8507 ± 1.75

Rheological Studies

Rheological analyses showed that all formulations exhibited Herschel-Bulkley flow characteristics, a time-independent non-Newtonian flow type (Table 4). For all three formulations, the viscosity of the formulation solutions decreased with increasing shear stress, independent of the active ingredient content. When the nanofiber formulation solutions were taken into the injector immediately after preparation, a highly viscous profile was encountered and was observed to flow rapidly through the column in the electrospinning device (Carrasco-Venegas et al., 2023; Hapipi et al., 2020; Mousazadeh et al., 2016).

In vitro Characterisation of Nanofiber Formulations

FESEM Imaging

The morphologies of the produced nanofibers were examined by FESEM analysis and the fibre diameters of the formulations coded N69, N78 and N79 were determined as 159 - 177 nm in accordance with the literature (AbdullahShukry et al., 2014). Although the distance between the tip from which the solution exits and the collector was 60 mm greater in N79 than in N78, no significant change in the nanofiber diameter was observed (Figure 3). Although there are studies in which the diameter decreased with increasing distance (Shahizam et al., 2020), a study with PVA revealed that the distance did not significantly change the diameter (Zhang et al., 2005). The diameter of the N69 formulation containing chloroform was relatively smaller (Figure 3). The voltage of N79 produced at the same distance was 23 kV, while for N69 it was 20 kV (Table 3). There are several conflicting reports in the literature regarding the effect of the applied high voltage on fibre morphology. In general, it is reported that higher voltage stretches the solution more and leads to finer fibres (Buchko et al.,1999; Lee et al., 2004). However, there is also a study showing that due to the increased potential difference with high voltage, the solution reaches the collector faster, thus forming larger diameter fibres (Demir et. al, 2002).

DSC Analysis

DSC analysis of the nanofiber samples showed sharp peaks in the range 301.0 °C - 319.2 °C. The melting point of 197.73 °C for OLZ was outside this range (Figure 4). This indicates that in all formulations, the active ingredient was entrapped in the polymer matrix (Ghasemian et al., 2013). This can be explained by the difference in the experimental and theoretical glass transition temperatures due to the strong hydrogen bonds between PVA and OLZ (Quan et al., 2020).

XRD Mapping

XRD analysis of the OLZ-PVA powder blend showed that OLZ completely retained its characteristic peaks. The same was observed in the XRD mapping of N69 and N79 (Figure 5). This indicated that the electrospinning process affected the crystal structure of PVA (Wang et al., 2024). Rapid evaporation and stretching of the solvent and rapid solidification of the polymer chains during the electrospinning process may prevent crystallisation and facilitate the formation of amor-

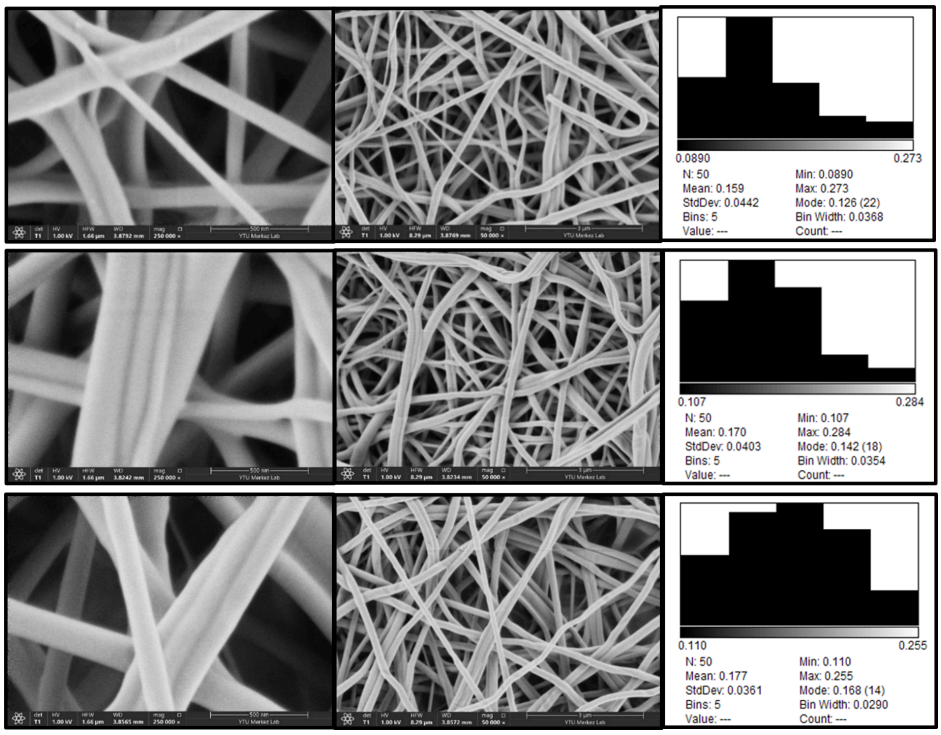

Figure 3. FESEM imaging findings at 250,000x and 50,000x magnification (n = 50) (From top to bottom: N69, N78 and N79).

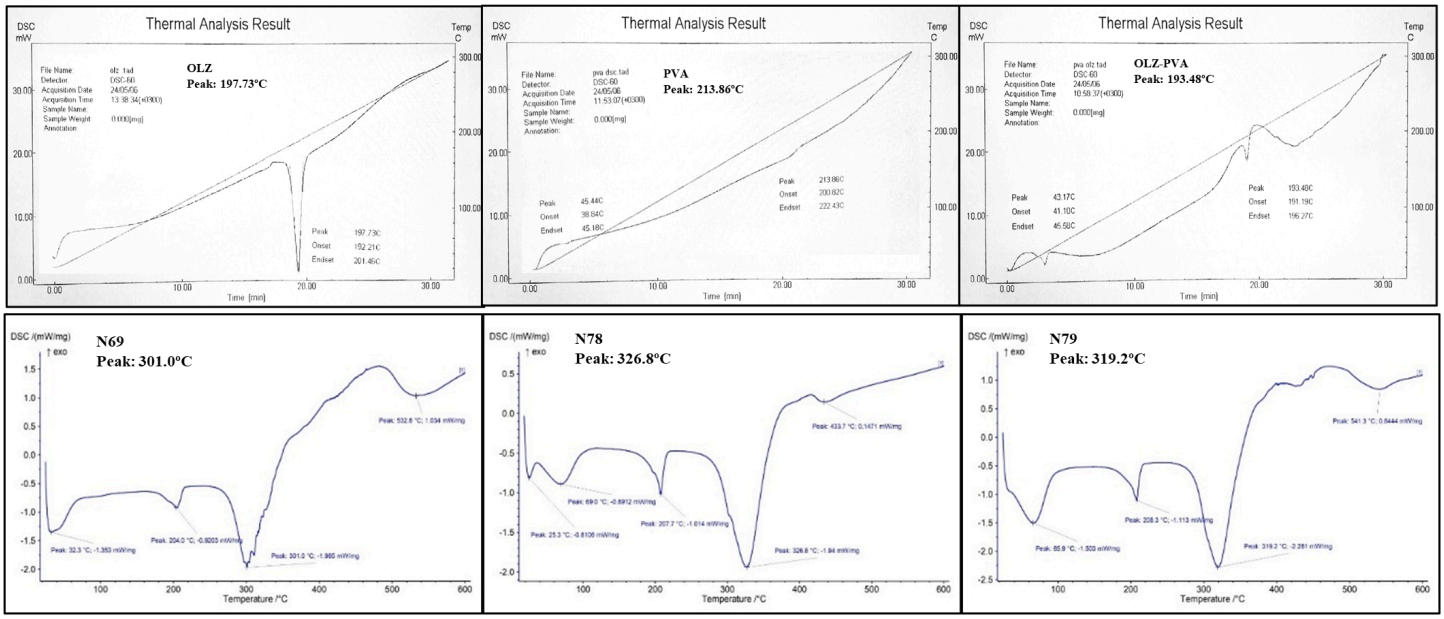

Figure 4. Results graphs of the DSC analysis (from left to right: OLZ, N69, PVA, N78, OLZ-PVA and N79). (DSC: Differential scanning calorimetry; OLZ: Olanzapine; PVA: Polyvinyl alcohol)

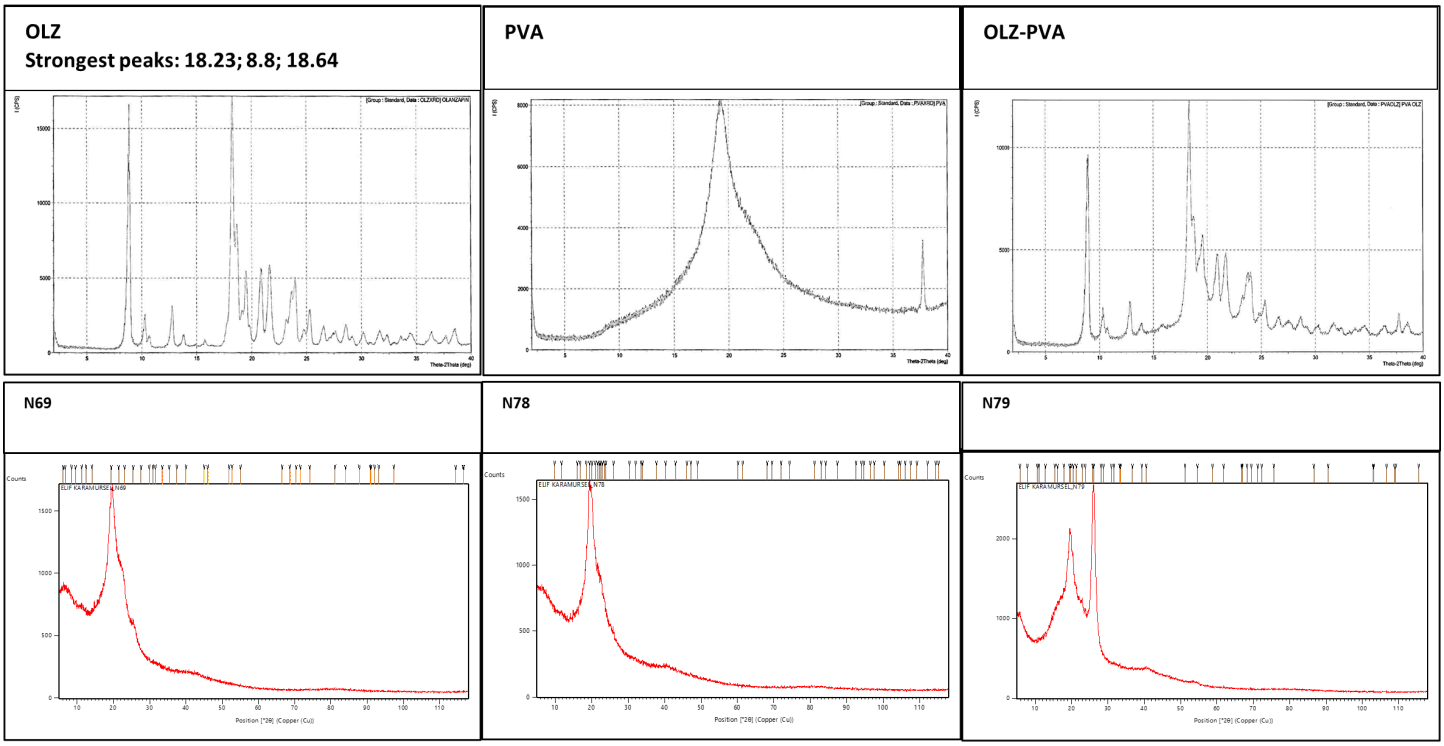

Figure 5. Results graphs of XRD analysis (n = 3) (From left to right: OLZ, N69, PVA, N78, OLZ-PVA and N79). (XRD: X-ray diffraction; OLZ: olanzapine; PVA: polyvinyl alcohol).

phous structures. The intense peaks of the N78 gave similar results to the XRD mapping of the pure PVA powder. This can be explained by the high encapsulation rate in the N78, which was produced at a lower voltage at a closer distance compared to other formulations (Ajiboye et al., 2021; Koosha & Mirzadeh, 2015). The fact that OLZ remains in amorphous form after incorporation into the nanofiber matrix will lead to an increase in its water solubility (Badgujar et al., 2024). Indeed, the solubility of N78 was found to be better than that of N69 and N79 (Figure 7).

FTIR Analysis

FTIR analysis was performed to investigate the chemical structure of the nanofibers and to examine the potential interactions between OLZ and PVA (Liu et al., 2019; Mundhe et al., 2013; Quan et al., 2020; Tunç et al., 2023). For OLZ, characteristic

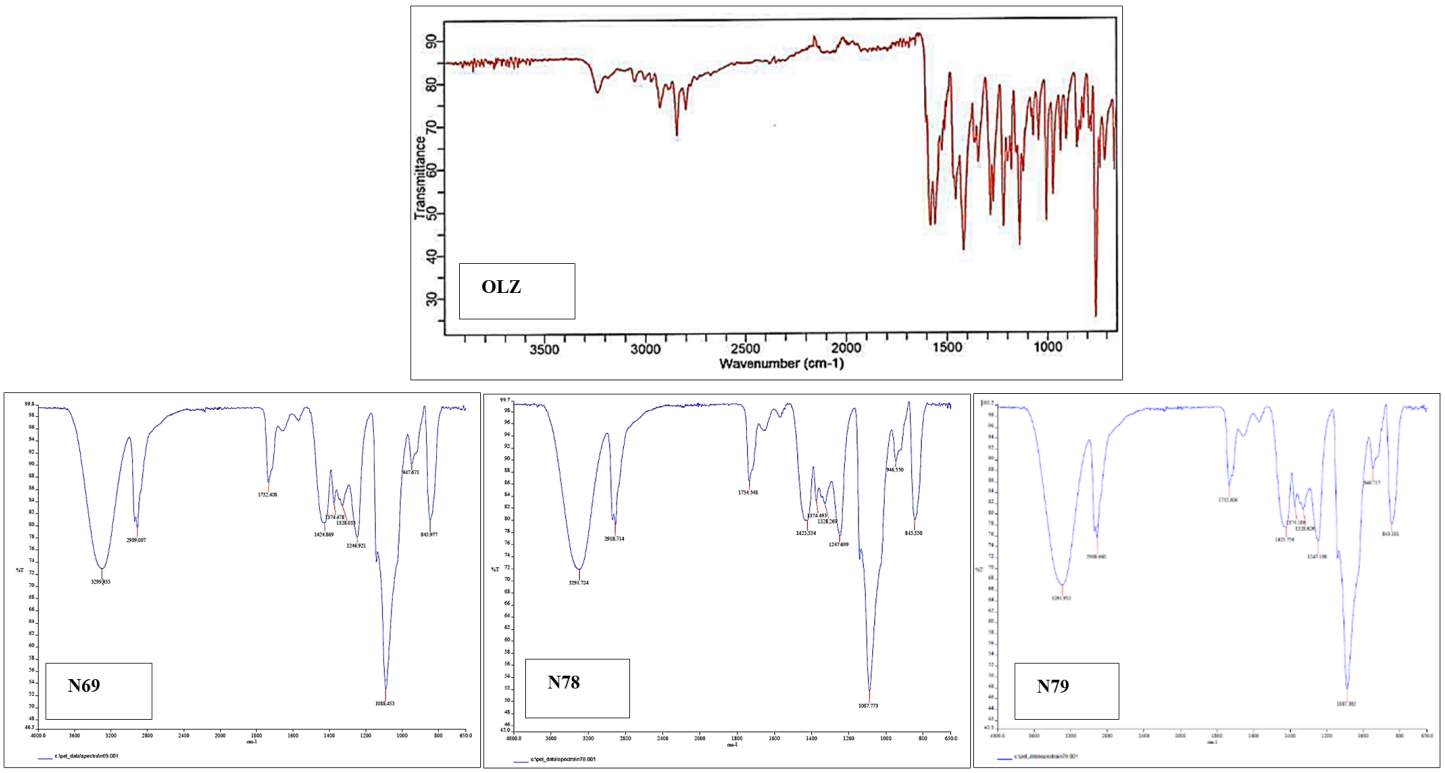

Figure 6. Results graphs of FTIR analysis (n = 3) (From left to right: OLZ (NH at 3200 - 3300 cm^{-1}; C-H at 2900 - 3000 cm^{-1}; C-H at 2800 - 2900 cm^{-1}; C-H at 2700 - 2800 cm^{-1}; C=C at 1500 - 1600 cm^{-1}; C=N at 1400 - 1500 cm^{-1}; C-N at 1200 - 1300 cm^{-1}), N69 (3299; 2909; 1932; 1424; 1374; 1374; 1328; 1246; 1088; 947; 845), N78 (3291; 2908; 1734; 1423; 1374; 1328; 1247; 1087; 946; 845) and N79 (3291; 2908; 1732; 1423; 1374; 1328; 1247; 1087; 946; 843)).

-NH, C-H, C-H, C=C, C=C, C=C, C=N and C-N stretching bands were observed in accordance with the literature (Figure 6) (Salem et al., 2015). In all three formulations analysed by FTIR, characteristic peaks representing C=O carbonyl stretching of the PVA polymer, C-O stretching of the acetyl groups and C-C were observed in accordance with the literature (Quan et al., 2020). The C-H and C=N peaks of the OLZ active substance were observed as smaller voltage bands. This can be explained by the lower presence of the active substance compared to the polymer and the encapsulation of the active substance in the polymer matrix (Karczewski et al., 2018).

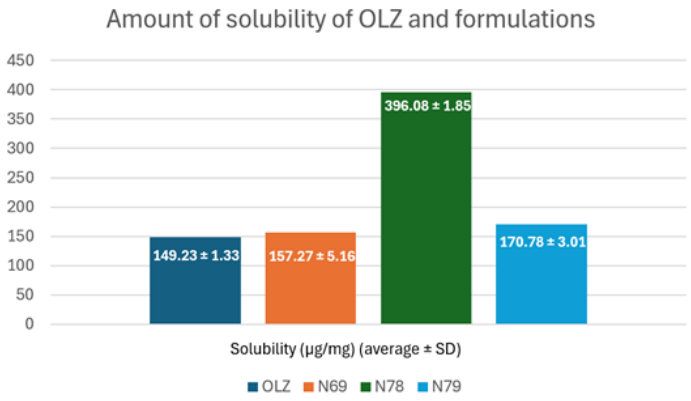

Figure 7. The solubility analysis of OLZ and formulations coded N69, N78 and N79 in pH 7.4 phosphate buffer (n = 3). (OLZ: Olanzapine)

Yield and Encapsulation Efficiency

Determining the amount of OLZ in the nanofibers and the loading efficiency was one of the most challenging parts of this study. Due to the inhomogeneous distribution of the active ingredient in the nanofiber production outputs, the quantification and loading efficiency determinations were repeated many times (Table 5). To obtain correlated results, quantification was performed with samples taken from the centre of the produced nanofiber layer (Morina et al., 2023; Szymańska et al., 2022). Looking at the loading efficiencies for all three formulations, it is seen that the most successful result belongs to the formulation coded N78 with a loading capacity of ~80.4%. The loading efficiency of N78, where the distance between the collector and the nozzle was less, was significantly higher than that of N79, where the distance was greater. For N79, this value is ~9.8%. It can be thought that the increase in the distance increases the scattering on the nanofiber, creating changes in the loading efficiency due to the nanofiber layer being spread over a larger area. Although the homogeneity was quite problematic, the loading efficiency of N69 was found to be higher than N79 (~29%). Considering that the shots were fired from the same distance, it was interpreted that the difference in the organic solvent used and the inhomogeneous distribution of the active substance may have caused this difference.

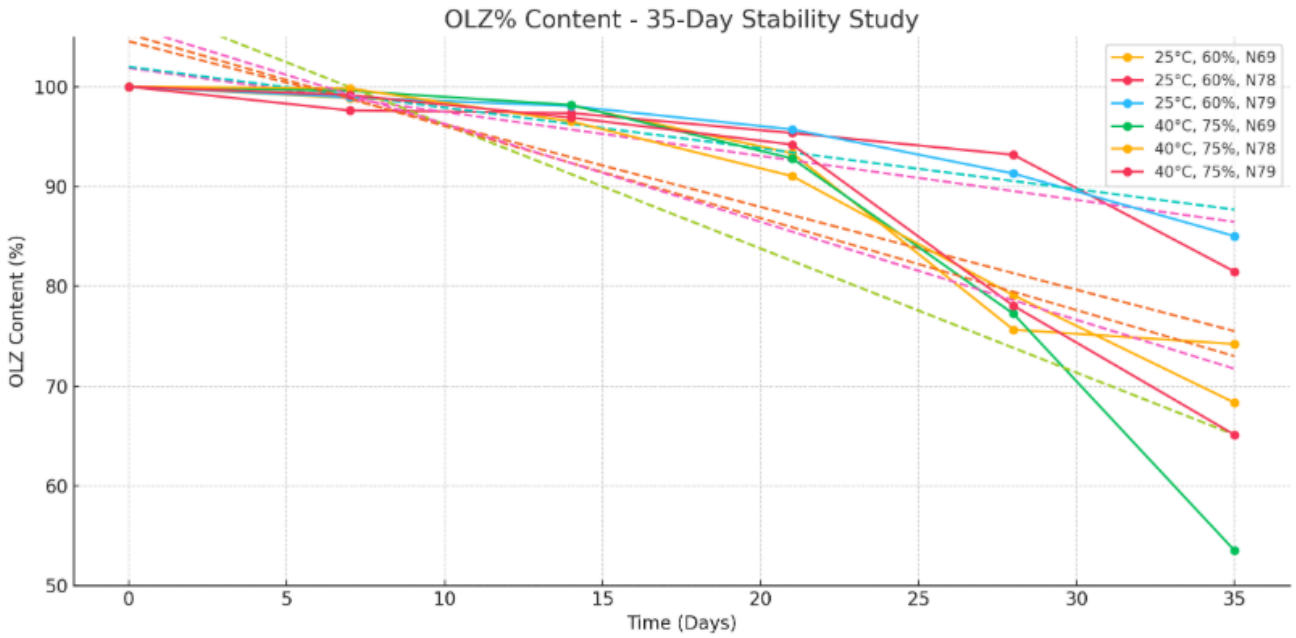

Figure 8. OLZ% content results of the 35-day stability study of all formulations coded N69, N78 and N79 at "25 ± 2 oC, 60 ± 5%" and "40 ± 2 oC, 75 ± 5%" relative humidity (n = 3)

In vitro Solubility Study

The formulation coded N78 showed approximately 2.65 times the solubility of pure OLZ. The solubility of the N79, which differs from the N78 with the electrospinning process parameters, is lower (Figure 7). The reason why N79 produced with the process parameters of 23 kV, 0.6 mL/h, 180 mm showed lower solubility than N78 produced with the process parameters of 18 kV, 0.5 mL/h, 120 mm can be associated with the effect of the process parameters on the nanofiber loading capacity. It is observed that in low-voltage production compared to high voltage, the fibres are bead-free and straighter fibres are formed as the distance decreases (Figure 2). Considering the diameters of the formed fibres (Figure 3), N78 and N79 have similar dimensions. This difference in solubility may be proportional to the difference in the loading capacities of the formulations (Q. Zhang et al., 2020). The solubility of the N69, which was smaller in diameter compared to N78 and N79, had lower solubility than the others. While the decrease in diameter was expected to contribute positively to the solubility by increasing the surface area, results close to pure OLZ solubility were obtained for the N69. The lower solubility of the N69 compared to the other formulations was explained by the low loading efficiency of the active substance (Figure 7) and the lack of homogeneous distribution in the nanofiber layer.

Stability Studies

The physical appearances of the nanofiber formulations N69, N78, and N79 were evaluated on days 7, 14, 21, and 35, showing no changes in colour or morphology throughout the 35-day stability study at 25 ± 2 °C, 60 ± 5% RH and 40 ± 2°C, 75 ± 5% RH. The diameter and thickness measurements remained consistent with the initial values (6 mm diameter; thickness: 0.2 mm for N69 and N79, 0.4 mm for N78).

The changes in the weights of the formulations during the 35-day stability study are shown in Table 6. While it was expected that significant weight changes due to degradation would be observed at 40 ± 2 °C, 75 ± 5% RH, only the weight change at 25 ± 2 °C, 60 ± 5% RH was found to be significant for formulations coded N78 and N79. The changes in weight can be interpreted as solvent evaporation or moisture absorption.

Stability studies were continued until the OLZ content of the nanofiber formulations decreased below 90%. The graph of the change in OLZ% contents with respect to time is shown in Figure 8. The OLZ contents in the formulations decreased with respect to time as expected. It was observed that the OLZ amounts decreased in a shorter time compared to other formulations, especially in the formulation coded N69. It was interpreted that this diversity of results may be due to the fact that dichloromethane evaporates faster than chloroform (Oliveira et al., n.d.) and that this situation may result in the product to be obtained in nanofiber production having different porous properties and therefore different loading capacities.

The limited data obtained from the 35-day stability study revealed the necessity of detailed stability studies. For this purpose, it was decided to conduct a long-term stability study using moisture-protected primary packaging in future studies.

Table 6. Weight measurements of the N69, N78, and N79 formulations during a 35-day stability study under conditions of 25 ± 2 °C, 60 ± 5% RH and 40 ± 2 °C, 75 ± 5% RH

	25 ± 2 °C, 60 ± 5% RH Nanofiber Sample Weight (mg) (mean ± SD)			40 ± 2 °C, 75 ± 5% RH Nanofiber Sample Weight (mg) (mean ± SD)		
	N69	N78	N79	N69	N78	N79
Day 0	1.179 ± 0.08	1.572 ± 0.04	1.797 ± 0.05	1.232 ± 0.07	1.276 ± 0.09	1.455 ± 0.02
Day 7	1.182 ± 0.02	1.561 ± 0.06	1.786 ± 0.03	1.217 ± 0.02	1.254 ± 0.05	1.440 ± 0.00
Day 14	1.183 ± 0.07	1.559 ± 0.01	1.781 ± 0.00	1.216 ± 0.02	1.252 ± 0.03	1.444 ± 0.09
Day 21	1.193 ± 0.03	1.553 ± 0.02	1.775 ± 0.08	1.209 ± 0.01	1.227 ± 0.06	1.445 ± 0.01
Day 28	1.190 ± 0.01	1.540 ± 0.00	1.771 ± 0.01	1.212 ± 0.08	1.210 ± 0.00	1.439 ± 0.05
Day 35	1.183 ± 0.00	1.525 ± 0.00	1.741 ± 0.01	1.219 ± 0.04	1.003 ± 0.05	1.409 ± 0.03
p-value	0.2670	0.0013	0.0073	0.2240	0.5229	0.0589

CONCLUSION

To increase the solubility of OLZ, a BCS II molecule, electrospun nanofibers were produced with water-soluble polymers such as PVA and HPMC. With the successful production of the PVA nanofibers, optimised electrospinning process parameters were determined. It was observed that the productions using greaseproof paper as the collector and the nozzle as the solution outlet were optimised. Because the encapsulation study showed that the drug distribution in the nanofibers was consistent in the central region, samples taken from the centre of the nanofiber layer were used in characterisation studies. The selected final formulations were found to be more soluble in 7.4 phosphate buffer than pure OLZ.

Considering the results, this study is a preliminary study of an attempt to develop nanofiber formulations to enhance the solubility of OLZ in water. A review of the existing literature revealed that there is no OLZ-loaded nanofiber formulation. This aspect of the study shows that it involves innovative approaches. Further studies are needed to convert the formulations from the model drug to the final product.

Peer Review Externally peer-reviewed.

Author Contributions Conception/Design of Study- E.K., E.U., N.A., M.E.D.; Data acquisition- E.K., E.U., N.A.; Data Analysis/Interpretation- E.K., E.U., N.A.; Drafting Manuscript- E.K., M.E.D.; Final Approval and Accountability- E.K., E.U., N.A., M.E.D., Y.Ö.

Conflict of Interest The authors declare that there are no conflicts of interest.

Grant Support The authors declared that this study has received no financial support.

Author Details

Elif Karamürsel
[1] İstanbul University, Faculty of Pharmacy, Department of Pharmaceutical Technology, İstanbul, Türkiye
0009-0000-3782-4036 elifkaramursel@gmail.com

Egemen Uzel
[2] İstanbul Yeni Yüzyıl University, Faculty of Pharmacy, Department of Pharmaceutical Technology, İstanbul, Türkiye
0000-0002-8658-3723

Neriman Aydilek
[1] İstanbul University, Faculty of Pharmacy, Department of Pharmaceutical Technology, İstanbul, Türkiye
0000-0002-8449-548X

Meltem Ezgi Durgun
[3] İstanbul Health and Technology University, Faculty of Pharmacy, Department of Pharmaceutical Technology, İstanbul, Türkiye
0000-0001-5724-9809

Yıldız Özsoy
[1] İstanbul University, Faculty of Pharmacy, Department of Pharmaceutical Technology, İstanbul, Türkiye
0000-0002-9110-3704

REFERENCES

Abdullah@Shukry, N. A., Ahmad Sekak, K., Ahmad, M. R., & Bustami Effendi, T. J. (2014). Characteristics of Electrospun PVA-Aloe vera Nanofibres Produced via Electrospinning. In *Proceedings of the International Colloquium in Textile Engineering, Fashion, Apparel and Design 2014 (ICTEFAD 2014)* (pp. 7–11). Springer Singapore. https://doi.org/10.1007/978-981-287-011-7_2

Acik, G. (2020). A comprehensive study on electrospinning of poly (Vinyl alcohol): Effects of the tcd, applied voltage, flow rate, and solution concentration. *Journal of the Turkish Chemical Society, Section A: Chemistry*, *7*(2), 609–616. https://doi.org/10.18596/jotcsa.741452

Ajiboye, A. L., Nandi, U., Galli, M., & Trivedi, V. (2021). Olanzapine loaded nanostructured lipid carriers via high shear homogenization and ultrasonication. *Scientia Pharmaceutica*, *89*(2). https://doi.org/10.3390/scipharm89020025

Al-Hazeem, N. Z. A. (2018). Nanofibers and Electrospinning Method. In *Novel Nanomaterials - Synthesis and Applications*. InTech. https://doi.org/10.5772/intechopen.72060

Badgujar, P., Malik, A. K., Mehata, A. K., Setia, A., Verma, N., Randhave, N., Shukla, V. N., Kande, V., Singh, P., Tiwari, P., Mahto, S. K., & Muthu, M. S. (2024). Polyvinyl alcohol-chitosan loaded oleanolic acid nanofibers against bacterial infection: *In vitro* studies and in-vivo evaluation by optical and laser Doppler imaging modalities. *International Journal of Biological Macromolecules*, 135532. https://doi.org/10.1016/j.ijbiomac.2024.135532

Barhoum, A., Rasouli, R., Yousefzadeh, M., Rahier, H., & Bechelany, M. (2019). Nanofiber Technologies: History and Development. In *Handbook of Nanofibers* (pp. 3–43).

Springer International Publishing. https://doi.org/10.1007/978-3-319-53655-2_54

Bhardwaj, N., & Kundu, S. C. (2010). Electrospinning: A fascinating fiber fabrication technique. In *Biotechnology Advances* (Vol. 28, Issue 3, pp. 325–347). https://doi.org/10.1016/j.biotechadv.2010.01.004

Buchko, C. J., Chen, L. C., Shen, Y., & Martin, D. C. (n.d.). *Processing and microstructural characterization of porous biocompatible protein polymer thin films*.

Cardenas Bates, I. I., Loranger, É., & Chabot, B. (2020). Chitosan-PEO nanofiber mats for copper removal in aqueous solution using a new versatile electrospinning collector. *SN Applied Sciences*, *2*(9). https://doi.org/10.1007/s42452-020-03342-5

Carrasco-Venegas, L. A., González-Fernández, J. V., Castañeda-Pérez, L. G., Palomino-Hernández, G., Dueñas-Dávila, F. A., & Trujillo-Pérez, S. A. (2023). Viscosity Factor (VF) Complementary to the Statistical Indicators Associated with the Rheological Behavior of Aqueous Solutions of Polyvinyl Alcohol. *Polymers*, *15*(7). https://doi.org/10.3390/polym15071743

Chauhan, I., Yasir, M., Verma, M., & Singh, A. P. (2020). Nanostructured lipid carriers: A groundbreaking approach for transdermal drug delivery. In *Advanced Pharmaceutical Bulletin* (Vol. 10, Issue 2, pp. 150–165). Tabriz University of Medical Sciences. https://doi.org/10.34172/apb.2020.021

Chen, H., Chen, S., Guan, Y., Yan, H., Jin, R., Zhang, H., Li, D., Zhong, J., & Li, L. (2017). An efficient polymer for producing electrospun transparent conducting films through simple procedures and a mild post-process. *RSC Advances*, *7*(74), 46621–46628. https://doi.org/10.1039/c7ra08520f

Das, B., Baidya, A. T. K., Mathew, A. T., Yadav, A. K., & Kumar, R. (2022). Structural modification aimed for improving solubility of lead compounds in early phase drug discovery. In *Bioorganic and Medicinal Chemistry* (Vol. 56). Elsevier Ltd. https://doi.org/10.1016/j.bmc.2022.116614

Demir, M. M., Yilgor, I., Yilgor, E., & Erman, B. (n.d.). *Electrospinning of polyurethane ®bers*. www.elsevier.com/locate/polymer

Fatahian, R., Mirjalili, M., Khajavi, R., Rahimi, M. K., & Nasirizadeh, N. (2021). Effect of electrospinning parameters on production of polyvinyl alcohol/polylactic acid nanofiber using a mutual solvent. *Polymers and Polymer Composites*, *29*(9_suppl), S844–S856. https://doi.org/10.1177/09673911211027126

Fathollahipour, S., Abouei Mehrizi, A., Ghaee, A., & Koosha, M. (2015). Electrospinning of PVA/chitosan nanocomposite nanofibers containing gelatin nanoparticles as a dual drug delivery system. *Journal of Biomedical Materials Research - Part A*, *103*(12), 3852–3862. https://doi.org/10.1002/jbm.a.35529

Ferreira, M. D., Duarte, J., Veiga, F., Paiva-Santos, A. C., & Pires, P. C. (2023). Nanosystems for Brain Targeting of Antipsychotic Drugs: An Update on the Most Promising Nanocarriers for Increased Bioavailability and Therapeutic Efficacy. In *Pharmaceutics* (Vol. 15, Issue 2). MDPI. https://doi.org/10.3390/pharmaceutics15020678

Garcia, J., Felix, M., Cordobés, F., & Guerrero, A. (2022). Effect of solvent and additives on the electrospinnability of BSA solutions. *Colloids and Surfaces B: Biointerfaces*, *217*. https://doi.org/10.1016/j.colsurfb.2022.112683

Ghasemian, E., Vatanara, A., Najafabadi, A. R., Rouini, M. R., Gilani, K., & Darabi, M. (2013). *Preparation, characterization and optimization of sildenafil citrate loaded PLGA nanoparticles by statistical factorial design*. http://www.darujps.com/content/21/1/68

Ghasemiyeh, P., & Mohammadi-Samani, S. (2018). Solid lipid nanoparticles and nanostructured lipid carriers as novel drug delivery systems: applications, advantages and disadvantages. In *Research in Pharmaceutical Sciences* (Vol. 13, Issue 4).

Gugulothu, D., Barhoum, A., Nerella, R., Ajmer, R., & Bechelany, M. (2019). Fabrication of Nanofibers: Electrospinning and Non-electrospinning Techniques. In *Handbook of Nanofibers* (pp. 45–77). Springer International Publishing. https://doi.org/10.1007/978-3-319-53655-2_6

Gupta, D., Jassal, M., & Agrawal, A. K. (2016). The electrospinning behavior of poly(vinyl alcohol) in DMSO-water binary solvent mixtures. *RSC Advances*, *6*(105), 102947–102955. https://doi.org/10.1039/c6ra15017a

Haddad, P., Brain, C., & Scott, J. (2014). Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. *Patient Related Outcome Measures*, 43. https://doi.org/10.2147/prom.s42735

Hapipi, N. M., Mazlan, S. A., Ubaidillah, U., Homma, K., Aziz, S. A. A., Nordin, N. A., Bahiuddin, I., & Nazmi, N. (2020). The rheological studies on poly(Vinyl) alcohol-based hydrogel magnetorheological plastomer. *Polymers*, *12*(10), 1–15. https://doi.org/10.3390/polym12102332

He, H., Kara, Y., & Molnar, K. (2019). Effect of needle characteristic on fibrous PEO produced by electrospinning. *Resolution and Discovery*, *4*(1), 7–11. https://doi.org/10.1556/2051.2018.00063

Józó, M., Simon, N., Yi, L., Móczó, J., & Pukánszky, B. (2021). Improved Release of a Drug with Poor Water Solubility by Using Electrospun Water-Soluble Polymers as Carriers. *Pharmaceutics*, *2022*, 34. https://doi.org/10.3390/pharmaceutics

Kajdič, S., Zupančič, Š., Roškar, R., & Kocbek, P. (2020). The potential of nanofibers to increase solubility and dissolution rate of the poorly soluble and chemically unstable drug lovastatin. *International Journal of Pharmaceutics*, *573*. https://doi.org/10.1016/j.ijpharm.2019.118809

Karczewski, A., Feitosa, S. A., Hamer, E. I., Pankajakshan, D., Gregory, R. L., Spolnik, K. J., & Bottino, M. C. (2018). Clindamycin-modified Triple Antibiotic Nanofibers: A Stain-free Antimicrobial Intracanal Drug Delivery System. *Journal of Endodontics*, *44*(1), 155–162. https://doi.org/10.1016/j.joen.2017.08.024

Khallaf, R. A., Aboud, H. M., & Sayed, O. M. (2020). Surface modified niosomes of olanzapine for brain targeting via nasal route; preparation, optimization, and in vivo evaluation. *Journal of Liposome Research*, *30*(2), 163–173. https://doi.org/10.1080/08982104.2019.1610435

Khan, K. U., Minhas, M. U., Badshah, S. F., Sohail, M., & Sarfraz, R. M. (2022). β-cyclodextrin modification by cross-linking polymerization as highly porous nanomatrices for olanzapine solubility improvement; synthesis, characterization and bio-compatibility evaluation. *Journal of Drug Delivery Science and Technology*, *67*. https://doi.org/10.1016/j.jddst.2021.102952

Kimya, A., Dalı, A., Danışmanı, T., & Kadioğlu, Y. (2014). *ATİPİK ANTİPSİKOTİK BİR İLAÇ OLAN OLANZAPİN'İN FARMASÖTİK PREPARATLARDA VE BİYOLOJİK ORTAMLARDA BİYOANALİTİK YÖNTEM VALİDASYONU Mevlüt ALBAYRAK*.

Koosha, M., & Mirzadeh, H. (2015). Electrospinning, mechanical properties, and cell behavior study of chitosan/PVA nanofibers. *Journal of Biomedical Materials Research - Part A*, *103*(9), 3081–3093. https://doi.org/10.1002/jbm.a.35443

Lee, J. S., Choi, K. H., Ghim, H. Do, Kim, S. S., Chun, D. H., Kim, H. Y., & Lyoo, W. S. (2004). Role of molecular weight of atactic poly(vinyl alcohol) (PVA) in the structure and properties of PVA nanofabric prepared by electrospinning. *Journal of Applied Polymer Science*, *93*(4), 1638–1646. https://doi.org/10.1002/app.20602

Liu, M., Zhang, Y., Sun, S., Khan, A. R., Ji, J., Yang, M., & Zhai, G. (2019). Recent advances in electrospun for drug delivery purpose. In *Journal of Drug Targeting* (Vol. 27, Issue 3, pp. 270–282). Taylor and Francis Ltd. https://doi.org/10.1080/1061186X.2018.1481413

Löbmann, K., & Svagan, A. J. (2017). Cellulose nanofibers as excipient for the delivery of poorly soluble drugs. *International Journal of Pharmaceutics*, *533*(1), 285–297. https://doi.org/10.1016/j.ijpharm.2017.09.064

Marano, S., Barker, S. A., Raimi-Abraham, B. T., Missaghi, S., Rajabi-Siahboomi, A., & Craig, D. Q. M. (2016). Development of micro-fibrous solid dispersions of poorly water-soluble drugs in sucrose using temperature-controlled centrifugal spinning. *European Journal of Pharmaceutics and Biopharmaceutics*, *103*, 84–94. https://doi.org/10.1016/j.ejpb.2016.03.021

Martínez-Pérez, C. A. (2020). Electrospinning: A promising technique for drug delivery systems. In *Reviews on Advanced Materials Science* (Vol. 59, Issue 1, pp. 441–454). Walter de Gruyter GmbH. https://doi.org/10.1515/rams-2020-0041

Mata, G. C. da, Morais, M. S., Oliveira, W. P. de, & Aguiar, M. L. (2022). Composition Effects on the Morphology of PVA/Chitosan Electrospun Nanofibers. *Polymers*, *14*(22). https://doi.org/10.3390/polym14224856

Meftah, A. M., Deckler, E., Citrome, L., & Kantrowitz, J. T. (2020). New discoveries for an old drug: a review of recent olanzapine research. In *Postgraduate Medicine* (Vol. 132, Issue 1, pp. 80–90). Taylor and Francis Inc. https://doi.org/10.1080/00325481.2019.1701823

Morina, E., Dotter, M., Döpke, C., Kola, I., Spahiu, T., & Ehrmann, A. (2023). Homogeneity of Needleless Electrospun Nanofiber Mats. *Nanomaterials*, *13*(18). https://doi.org/10.3390/nano13182507

Mousazadeh, S., Shakouri, A., Hojjat, M., Etemad, S. G., & Heris, S. Z. (2016). Rheological behavior of starch–poly(vinyl alcohol)–TiO2 nanofluids and their main and

interactive effects. *Journal of Applied Polymer Science*, *133*(41). https://doi.org/10.1002/app.44062

Mundhe, M. V., Vinayakmundhe, M., Burande, S., Kondapure, M. A., Vilas Arsul, M., & Zarekar, S. (2013). Formulationand Evaluation of Mouth Dissolving Tablet of Olanzapine by Coprocessing Superdisintegrants. In *Asian Journal of Pharmaceutical Technology & Innovations* (Issue 01). www.asianpharmtech.com

Naseri, N., Mathew, A. P., Girandon, L., Fröhlich, M., & Oksman, K. (2015). Porous electrospun nanocomposite mats based on chitosan–cellulose nanocrystals for wound dressing: effect of surface characteristics of nanocrystals. *Cellulose*, *22*(1), 521–534. https://doi.org/10.1007/s10570-014-0493-y

Natarajan, J., Baskaran, M., Humtsoe, L. C., Vadivelan, R., & Justin, A. (2017). Enhanced brain targeting efficacy of Olanzapine through solid lipid nanoparticles. *Artificial Cells, Nanomedicine and Biotechnology*, *45*(2), 364–371. https://doi.org/10.3109/21691401.2016.1160402

Ojha, S. S. (2007). *Fabrication and Characterization of Novel Single and Bicomponent Electrospun Nanofibrous Mats*. Faculty of North Carolina State University.

Oliveira, J., Silveira Brichi, G., Marconcini, J. M., Mattoso, H. C., Glenn, G. M., Medeiros, S., & Oliveira, J. (n.d.). Effect of Solvent on The Physical and Morphological Properties of Poly(Lactic Acid) Nanofibers Obtained by Solution Blow Spinning. In *Journal of Engineered Fibers and Fabrics* (Vol. 117). http://www.jeffjournal.org

Paaver, U., Heinämäki, J., Kassamakov, I., Ylitalo, T., Hæggström, E., Laidmäe, I., & Kogermann, K. (2019). Quasi-dynamic dissolution of electrospun polymeric nanofibers loaded with piroxicam. *Pharmaceutics*, *11*(10). https://doi.org/10.3390/pharmaceutics11100491

Paaver, U., Heinämäki, J., Laidmäe, I., Lust, A., Kozlova, J., Sillaste, E., Kirsimäe, K., Veski, P., & Kogermann, K. (2015). Electrospun nanofibers as a potential controlled-release solid dispersion system for poorly water-soluble drugs. *International Journal of Pharmaceutics*, *479*(1), 252–260. https://doi.org/10.1016/j.ijpharm.2014.12.024

Pattnaik, S., Swain, K., & Ramakrishna, S. (2023). Optimal delivery of poorly soluble drugs using electrospun nanofiber technology: Challenges, state of the art, and future directions. In *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology* (Vol. 15, Issue 2). John Wiley and Sons Inc. https://doi.org/10.1002/wnan.1859

Pelipenko, J., Kocbek, P., & Kristl, J. (2015). Critical attributes of nanofibers: Preparation, drug loading, and tissue regeneration. In *International Journal of Pharmaceutics* (Vol. 484, Issues 1–2, pp. 57–74). Elsevier. https://doi.org/10.1016/j.ijpharm.2015.02.043

Potrč, T., Baumgartner, S., Roškar, R., Planinšek, O., Lavrič, Z., Kristl, J., & Kocbek, P. (2015). Electrospun polycaprolactone nanofibers as a potential oromucosal delivery system for poorly water-soluble drugs. *European Journal of Pharmaceutical Sciences*, *75*, 101–113. https://doi.org/10.1016/j.ejps.2015.04.004

Quan, P., Wan, X., Tian, Q., Liu, C., & Fang, L. (2020). Dicarboxylic acid as a linker to improve the content of amorphous drug in drug-in-polymer film: Effects of molecular mobility, electrical conductivity and intermolecular interactions. *Journal of Controlled Release*, *317*, 142–153. https://doi.org/10.1016/j.jconrel.2019.11.033

Ramakrishnan, R., Gimbun, J., Ramakrishnan, P., Ranganathan, B., Reddy, S. M., & Shanmugam, G. (2019). Effect of solution properties and operating parameters on needleless electrospinning of poly (ethylene oxide) nanofibers loaded with bovine serum albumin. *Current Drug Delivery*, *16*(10), 913–922.

Rošic, R., Pelipenko, J., Kristl, J., Kocbek, P., Bešter-Rogač, M., & Baumgartner, S. (2013). Physical characteristics of poly (vinyl alcohol) solutions in relation to electrospun nanofiber formation. *European Polymer Journal*, *49*(2), 290–298. https://doi.org/10.1016/j.eurpolymj.2012.11.013

Salem, H. F., Mahmoud Abdelhaleem Ali, A., Mohamed, E., Elbary, A. A., A Ali, A. M., & Maher, E. M. (2015). Formulation and in-vitro evaluation of fast dissolving tablets containing a poorly soluble antipsychotic drug. In *International Journal of Drug Delivery* (Vol. 7). http://www.arjournals.org/index.php/ijdd/index

Savjani, K. T., Gajjar, A. K., & Savjani, J. K. (2012). Drug Solubility: Importance and Enhancement Techniques. *ISRN Pharmaceutics*, *2012*, 1–10. https://doi.org/10.5402/2012/195727

Shahizam, Z. A., Benoudjit, A. M., Mohamad, N., Abd-Wahab, F., Amani, W. W., & Salim, W. (2020). Morphology of electrospun PVA nanofibers enhanced with graphene oxide, poly (3,4-ethylenedioxythiophene): Polystyrene sulfonate (PEDOT:PSS) and multiwalled carbon nanotubes. In *Theo. Exp. NANOTECHOLOGY* (Vol. 4).

Sill, T. J., & von Recum, H. A. (2008). Electrospinning: Applications in drug delivery and tissue engineering. In *Biomaterials* (Vol. 29, Issue 13, pp. 1989–2006). https://doi.org/10.1016/j.biomaterials.2008.01.011

Singh, S. K., Hidau, M. K., Gautam, S., Gupta, K., Singh, K. P., Singh, S. K., & Singh, S. (2018). Glycol chitosan functionalized asenapine nanostructured lipid carriers for targeted brain delivery: Pharmacokinetic and teratogenic assessment. *International Journal of Biological Macromolecules*, *108*, 1092–1100. https://doi.org/10.1016/j.ijbiomac.2017.11.031

Szymańska, E., Wojasiński, M., Dąbrowska, J., Krzyżowska, M., Nowicka, M., Ciach, T., & Winnicka, K. (2022). Chitosan-poly(ethylene oxide) nanofibrous mat as a vaginal platform for tenofovir disoproxyl fumarate – The effect of vaginal pH on drug carrier performance. *International Journal of Biological Macromolecules*, *222*, 856–867. https://doi.org/10.1016/j.ijbiomac.2022.09.207

Tunç, E., Uğur Kaplan, A., Kilinboz, Y., & Çetin, M. (2023). Nanoemulsion formulation containing carbamazepine and levetiracetam: Development and *in vitro* characterization. *İstanbul Journal of Pharmacy*, *53*(2), 133–139. https://doi.org/10.26650/İstanbuljpharm.2023.1201106

Vashisth, P., Pruthi, P. A., Singh, R. P., & Pruthi, V. (2014). Process optimization for fabrication of gellan based electrospun nanofibers. *Carbohydrate Polymers*, *109*, 16–21. https://doi.org/10.1016/j.carbpol.2014.03.003

Verreck, G., Chun, I., Peeters, J., Rosenblatt, J., & Brewster, M. E. (2003). *Preparation and Characterization of Nanofibers Containing Amorphous Drug Dispersions Generated by Electrostatic Spinning*.

Vuddanda, P. R., Mathew, A. P., & Velaga, S. (2016). Electrospun nanofiber mats for ultrafast release of ondansetron. *Reactive and Functional Polymers*, *99*, 65–72. https://doi.org/10.1016/j.reactfunctpolym.2015.12.009

Wang, Y., Lv, H., Wang, C., He, D., Zhao, H., Xu, E., Jin, Z., Wu, Z., Liu, P., & Cui, B. (2024). Preparation of starch-based green nanofiber mats for probiotic encapsulation by electrospinning. *Journal of Food Science*. https://doi.org/10.1111/1750-3841.17250

Yosef Kinani, A. A. B., Hussein, A. A., & Alsaraf, K. M. (2022). Formulation and Characterization of Electrospun Nanofibers Loaded Fusidic Acid for Wound Dressing Technique. *Journal of Pharmaceutical Negative Results*, *13*(4), 221–233. https://doi.org/10.47750/pnr.2022.13.04.027

Zahmatkeshan, M., Adel, M., Bahrami, S., Esmaeili, F., Rezayat, S. M., Saeedi, Y., Mehravi, B., Jameie, S. B., & Ashtari, K. (2019). Polymer-Based Nanofibers: Preparation, Fabrication, and Applications. In *Handbook of Nanofibers* (pp. 215–261). Springer International Publishing. https://doi.org/10.1007/978-3-319-53655-2_29

Zhang, C., Yuan, X., Wu, L., Han, Y., & Sheng, J. (2005). Study on morphology of electrospun poly(vinyl alcohol) mats. *European Polymer Journal*, *41*(3), 423–432. https://doi.org/10.1016/j.eurpolymj.2004.10.027

Zhang, Q., Lin, Z., Zhang, W., Huang, T., Jiang, J., Ren, Y., Zhang, R., Li, W., Zhang, X., & Tu, Q. (2020). Fabrication of green poly(vinyl alcohol) nanofibers using natural deep eutectic solvent for fast-dissolving drug delivery. *RSC Advances*, *11*(2), 1012–1021. https://doi.org/10.1039/d0ra08755f

Zorkina, Y., Abramova, O., Ushakova, V., Morozova, A., Zubkov, E., Valikhov, M., Melnikov, P., Majouga, A., & Chekhonin, V. (2020). Nano Carrier Drug Delivery Systems for the Treatment of Neuropsychiatric Disorders: Advantages and Limitations. In *Molecules* (Vol. 25, Issue 22). MDPI. https://doi.org/10.3390/MOLECULES25225294