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*RESEARCH ARTICLE*

# Development and Characterization of Nanofiber Strip Containing Sertraline for Buccal Application

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***Development and Characterization of Nanofiber Strip Containing Sertraline for Buccal Application***

***SUMMARY***

*Sertraline is one of the selective serotonin reuptake inhibitors indicated in major depressive disorder. Schizophrenia is a mental disorder with frequent depressive symptoms. Sertraline is thought to be useful for the treatment of depressive symptoms in schizophrenia. The objective of this study is to formulate sertraline-containing nanofiber strips produced by the electrospinning process, that can be easily dispersed by the buccal route, suitable for the use of schizophrenia patients. Here, various ratios (5%,7.5%, and 10%) of polyvinyl pyrrolidone (PVP) polymer solutions were prepared, and electrical conductivity, viscosity, and surface tension characterization studies were performed on polymer solutions. After characterization studies, a polymer solution containing 5% PVP was selected to prepare nanofibers. Nanofibers were obtained using the electrospinning method, each strip containing 5 mg sertraline. It was observed that the chosen optimum formulation nanofiber had an average particle diameter of 371-439 nm in the SEM image. Tensile strength and elongation at break percentage values of 5% PVP-sertraline nanofibers values were 0.449±0.284 (Mpa) and 22.6±3.66 (%), respectively. The loading capacity and encapsulation efficiency of the formulation are 4.53±0.31% and 79.61±10.56%, respectively. In vitro drug dissolution studies showed that sertraline-containing buccal nanofibers conformed to the Hixson-Crowell kinetic model.*

***Key Words:*** *Nanofiber, electrospinning, sertraline, polyvinyl pyrrolidone (PVP), buccal strip*

***Bukkal Uygulamaya Yönelik Sertralin İçeren Nanofiber Şerit Geliştirilmesi ve Karakterizasyonu***

***ÖZ***

*Sertralin, majör depresif bozuklukta belirtilen seçici serotonin geri alım inhibitörlerinden biridir. Şizofreni, sık sık depresif belirtiler gösteren bir ruhsal bozukluktur. Sertralinin şizofrenide depresif semptomların tedavisinde faydalı olduğu düşünülmektedir. Bu çalışmanın amacı, şizofreni hastalarının kullanımına uygun, elektroeğirme işlemi ile üretilmiş, bukkal yolla kolaylıkla dağılabilen, sertralin içerikli nanolif stripler geliştirmektir. Burada çeşitli oranlarda (%5, %7.5 ve %10) polivinil pirolidon (PVP) polimer çözeltileri hazırlanmış ve polimer çözeltileri üzerinde elektriksel iletkenlik, viskozite ve yüzey gerilimi karakterizasyon çalışmaları yapılmıştır. Karakterizasyon çalışmalarından sonra, optimum nanolifleri hazırlamak için %5 PVP içeren bir polimer çözeltisi seçilmiştir. Her strip 5 mg sertralin içeren elektroeğirme yöntemi kullanılarak nanolifler elde edilmiştir. Optimum formülasyon seçilen nanofiberin SEM görüntüsünde ortalama 371-439 nm partikül çapına sahip olduğu gözlenmiştir. %5 PVP-sertralin nanoliflerinin gerilme direnci ve kopma yüzdesindeki uzama değerleri sırasıyla 0.449±0.284 (Mpa) ve 22.6±3.66 (%)'dir. Formülasyonun yükleme kapasitesi ve kapsülleme verimliliği sırasıyla %4.53±0.31 ve %79.61±10.56'dır. İn vitro ilaç çözünme hızı çalışmaları, sertralin içeren bukkal nanoliflerin Hixson-Crowell kinetik modeline uygun olduğunu göstermiştir.*

***Anahtar Kelimeler:*** *Nanolif, elektroeğirme, sertralin, polivinil pirolidon(PVP), bukkal şerit*

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## INTRODUCTION

Sertraline is one of the first selective serotonin reuptake inhibitors to be used and approved since the early 1990s. The serotonin transporter acts by increasing the higher extracellular level of serotonin (5-HT) as a result of 5-HT inhibition (Sanchez et al., 2014). It is indicated for major depressive disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, and social anxiety disorder (Singh & Saadabadi, 2019).

Schizophrenia is a combination of symptoms with an uncertain cause identified mainly, by indicators of a disorder called psychosis (Insel, 2010). Schizophrenia is characterized by both positive and negative symptoms, as well as cognitive impairment. Positive symptoms include hallucinations, delusions, and psychotic symptoms with a loss of contact with reality, and negative symptoms include a lack of spontaneity and motivation and social withdrawal (Merikangas et al., 2022). Depressive symptoms are frequently seen in schizophrenia. Depression is an important symptom, not only causing mental distress but also an increased risk of suicide and rehospitalization, worsening psychosocial outcomes. Sertraline is thought to be useful in the treatment of depressive symptoms in schizophrenia (Mulholland et al., 2003).

Buccal application has advantages such as protection of drugs from hepatic metabolism and enzyme degradation. (Laffleur & Röttges, 2019). Buccal strips can be applied without water and chewing. Due to its thin film structure, it dissolves more stable and faster than other conventional dosage forms. They are more easily administered than solid drug forms in geriatric, pediatric, and neurodegenerative patients (Pastório et al., 2021; Mahajan, 2012).

Electrospinning is a straightforward and dependable method for producing smooth nanofibers with variable shapes from various polymers (Xue et al., 2019). The solvent of polymer solution is evaporated by an electric field, and nanofiber formation is achieved (Ilbasmis-Tamer et al., 2022). The electrospinning method is used as an alternative to solvent evaporation, and hot melt extraction methods for preparing buccal thin strips. With the electrospinning method, the amorphous fibers, which have more flexibility and plasticity, also have high wettability and porosity (Pacheco et al., 2021; Qin et al., 2019).

Polyvinyl pyrrolidone (PVP, Povidone) is a hydrophilic polymer composed of N-vinyl pyrrolidone monomers. It is biocompatible, non-toxic, essentially chemically inert, stable in various temperature and pH values and non-ionic. PVP has good wettability and can form films quickly (Kurakula & Rao, 2020).

The objective of this study is to formulate nanofiber strips containing sertraline that can be easily dispersed by the buccal route, suitable for the use of schizophrenia patients. The reason for choosing buccal fiber containing sertraline is to increase drug-patient compliance in depressive periods of patients with schizophrenia. In the present study, nanofiber strips containing sertraline with different PVP concentrations were produced, and characterization studies were conducted. *In vitro* dissolution studies were performed using USP apparatus I on sertraline nanofibers.

## MATERIALS AND METHODS

### Chemicals

PVP is from BASF (Kollidon 90F®), and ethanol absolute is from Isolab Chemicals. Sertraline was obtained from Cipla Ltd. (Bombay, India).

### Preparation of Polymer Solutions

Sertraline and PVP were dissolved in ethanol using a magnetic stirrer at room temperature to create various nanofiber solutions. Due to its suitability as a solvent for both sertraline and PVP, ethanol was chosen as the electrospinning solvent. Different PVP concentrations (5%, 7.5%, and 10%) of polymer solutions were developed in order to reach the proper polymer concentration. Following optimization, regarding polymer concentration, a solubility study was carried out to determine suitable sertraline dose. Every prepared solution was characterized. The viscosity, conductivity, and surface tension parameters were measured and assessed to understand how solution components affect the solution's characteristics. Concentrations of polymer solutions are given in Table 1.

**Table 1.** Concentrations of different nanofiber solutions

| Formulations | PVP Concentration (w/v%) | Sertraline Amount (mg) |
|---|---|---|
| **F1** | 5 | - |
| **F2** | 7.5 | - |
| **F3** | 10 | - |
| **F4** | 5 | 5 |
| **F5** | 7.5 | 5 |

**Production of Nanofibers by Electrospinning Method**

Nanofibers were manufactured by electrospinning technique. The electrospinning equipment (Inovenso NE100)'s micro pump section was used to inject each solution into a 10 mL syringe. The surface of the collector is wrapped with aluminum foil, and nanofibers are gathered on the aluminum foil surface. Nanofibers were produced with these parameters; 2.5 mL/h feed rate, 19 kV voltage, 14 cm distance, and 8 h process time.

**Characterization Polymer Solutions and Nanofibers**

The viscosity, surface tension, and conductivity parameter values of polymer solutions were calculated to establish the optimum formulation. Viscosity was measured using a stress-controlled cone and plate rheometer (Brookfield, DV-III Rheometer with Spindle Type CPE-42, USA). Various speeds were used to measure the viscosity values. By producing droplets at the needle tip, the surface tension was measured by pendent drop observation (Attension-Theta Lite, Biolin Scientific, Finland). The Young Laplace Equation was used to determine the values derived from the samples. The conductivity values of the developed polymer solutions were measured using a conductivity meter (Hanna Instruments, HI 9033, USA). For each formulation, the measurement was carried out three times.

With using a texture analyzer (Stable Micro Systems, TA.XT. PlusTexture Analyzer, UK), the mechanical properties were assessed based on elongation at break value and tensile strength. In order to determine the tensile strength and elongation at break, three samples of each formulation were cut into 1 cm x 3 cm pieces. In addition to this analysis, an *ex vivo* mucoadhesion study was performed.

The buccal tissue was placed in a 50N load cell and wetted with pH 6.75 saliva buffer, and the formulation was contacted with the tissue with a mucoadhesive holder. The model tissue was buccal tissue from cows. Double-sided tape is used to secure the nanofiber to the probe's lower end. The contact time was set to 60 s, the applied force was set to 0.2 N, and the rate was set to 1 mm/s.

The morphology and diameter of nanofibers were analyzed with scanning electron microscopy (SEM) (JSM-6060).

**Loading Capacity and Encapsulation Efficiency**

Specific sizes of fiber were received from formulations made with sertraline dissolved in pH 6.75 buffer allowed estimations of loading capacity and encapsulation efficiency to be made against stock sertraline solution. In order to determine the specific wavelength of sertraline, the sertraline solution was scanned in a UV spectrophotometer, and the peak value was obtained at 235 nm. Therefore, the produced solutions' absorbances were determined at 235 nm. There were three samples made for each formulation.

### *In vitro* dissolution study

The dissolution study was performed using USP apparatus I (Agilent 708-DS, USA) on nanofiber formulations that contain sertraline. The study was conducted in a 250 mL 1:5 ethanol : pH 6.75 phosphate buffer environment at 37 °C and 50 rpm. Cut into 2 cm x 3 cm pieces; the nanofibers have been placed in baskets. Studies were triplicated for each formulation. At certain time points, a 5 mL sample was taken, and 5 mL dissolution medium was added to provide sink condition. Absorbance values were measured at 235 nm using a UV spectrophotometer.

As a result of this study, the kinetic models are calculated by using DDSolver Software. For the evaluation of models $r^2_{adj}$, AIC, and MSC parameters were used.

## RESULTS AND DISCUSSION

### Characterization of Polymer Solutions

Electrospinning of polymer solutions into nanofibers is influenced by solution properties such as viscosity, surface tension, and conductivity. (Li et al., 2013). For this reason, these three parameters were determined for each polymer solution that does not contain sertraline. After evaluating the results of these studies, the optimum polymer concentration was decided.

The results of surface tension and conductivity measurements are given in Table 2. As demonstrated in Table 2, the surface tension values obtained depending on the PVP ratio in the polymer solution and the addition of sertraline do not significantly differ from one another. In the study by Bolten and Türk, a surface tension comparison of PVP with different molecular weights and different concentrations was made. In PVP K90, which has a similar molecular weight to the Kollidon 90F we used in our study, surface tension decreased as the PVP concentration increased. They found that the reason is that impurities cause a sudden drop in certain PVP concentrations (Bolten & Türk, 2011). Probably Kollidon 90F, which we used in the study, contains trace amounts of impurities. The sertraline formulation is expected to have the lowest surface tension as it contains more impurities than the others.

High-viscosity solutions increase the risk of clogging the nozzles. Figures 1 and 2 show, respectively, the shear stress-shear rate and viscosity-shear rate profiles of the solutions produced. The solution containing 10% PVP in the polymer solutions without sertraline had the maximum viscosity. Hence, it was disregarded. The difference between the viscosity values of the polymer solution containing 7.5% PVP and the polymer solution containing 5% PVP is not significant. Despite changing certain parameters, a sufficient result could not be achieved when fiber production with a polymer solution containing 7.5% PVP was attempted. Therefore, it was decided that the suitable polymer solution was the solution contained 5% PVP. The addition of sertraline to this solution increased the viscosity, but this increase was not significant. Kotia et al., in their work, Shear stress-shear rate and shear rate-viscosity values of PVP solutions at different molecular weights and concentrations were investigated. The findings were consistent with our research. According to Figures 1 and 2, shearing stress and viscosity change in relation to shearing rate, with shearing stress increasing in Figure 1 and viscosity decreasing in Figure 2, respectively (Kotia et al., 2021)

The PVP ratio in the polymer solutions without sertraline affected the conductivity values. The resultant formulation, which contained 30 mg of sertraline and 5% PVP, had the highest conductivity score. Because of the availability of ionic substances in the polymer (mainly impurities or additions) rises when a polymer is dissolved in a solvent, the conductivity of the solution increases (Amariei et al., 2017). Since high conductivity is often sought for electrospinning, it was determined that the generated sertraline-containing polymer solution's conductivity value was suitable for the electrospinning method of producing nanofibers.

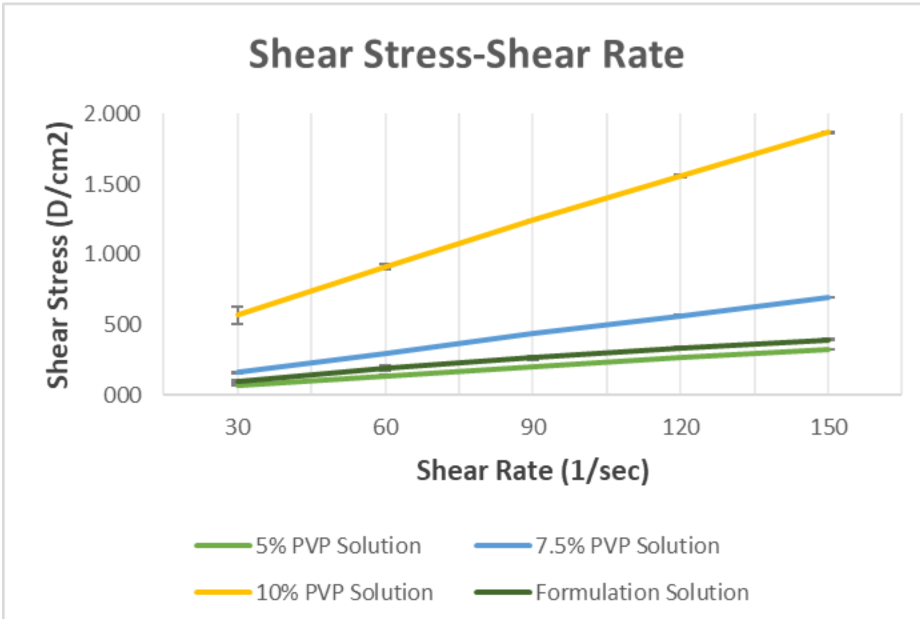


**Figure 1.** Shear stress-Shear rate profiles of polymer solutions and formulation solutions.

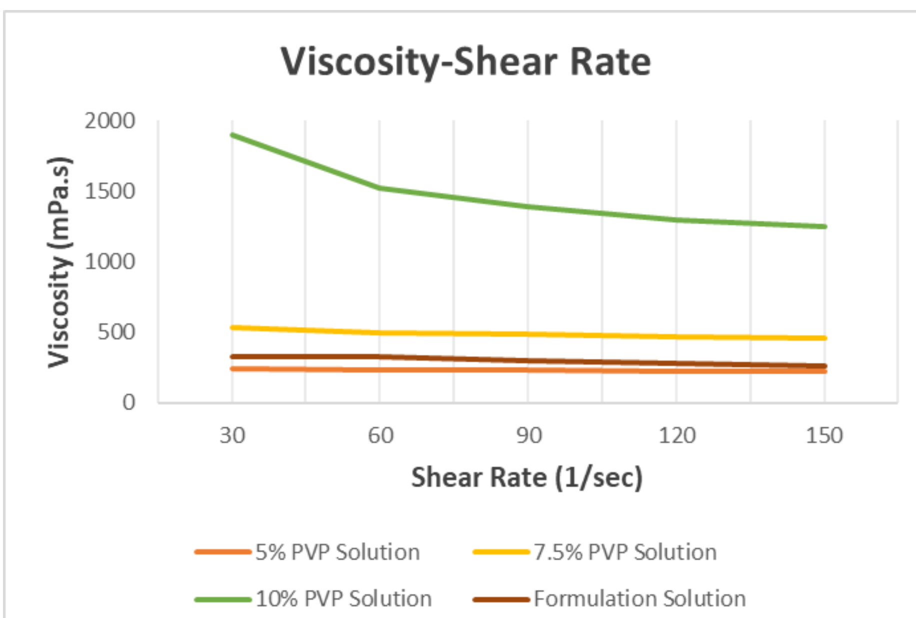


**Figure 2.** Viscosity-Shear rate profiles of polymer solutions and formulation solutions.

**Table 2.** Surface tension and conductivity values of all formulations (n±SD).

| Formulation | Surface Tension (mN/m) | Conductivity (µS/cm) |
|---|---|---|
| **5% PVP Solution** | 26.0±0.31 | 13.1±1.86 |
| **7.5%PVP Solution** | 26.4±1.16 | 17.0±1.07 |
| **10% PVP Solution** | 21.9±11.1 | 22.06±1.57 |
| **Formulation** | 20.7 ± 0.77 | 68.0±0.25 |

### Characterization of Nanofibers

SEM measurements were taken to study the surface morphology of nanofibers. The surface morphology of the blank nanofiber (sertraline-free nanofiber) and the resulting formulation are demonstrated in Figure 3. The surface of the nanofiber was observed in SEM images. Diameters of of blank nanofibers and resulting formulation are measured as 359 nm and 387 nm, respectively. According to the SEM pictures, the sertraline nanofibers' average diameter was found to be greater than that of the blank nanofibers. The average diameter increased with sertraline loading. In study by Puspuroni et al., 10% PVP nanofiber had an average fiber diameter ($D_{ave}$) of 563 nm (Pusporini et al., 2018). In a study by Demiröz et al., it was shown that PVP nanofibers' average diameters ranged from 445± 93 nm to 1752± 231 nm at higher concentrations (10, 12.5%, and 15% a/h). In the study, the average nanofiber diameter increased for all formulations as polymer concentration increased. For this reason, PVP we used at the rate of 5% in our study is expected to have a smaller average diameter than the results in the literature (Tuğcu-Demiröz et al., 2020).

A

B

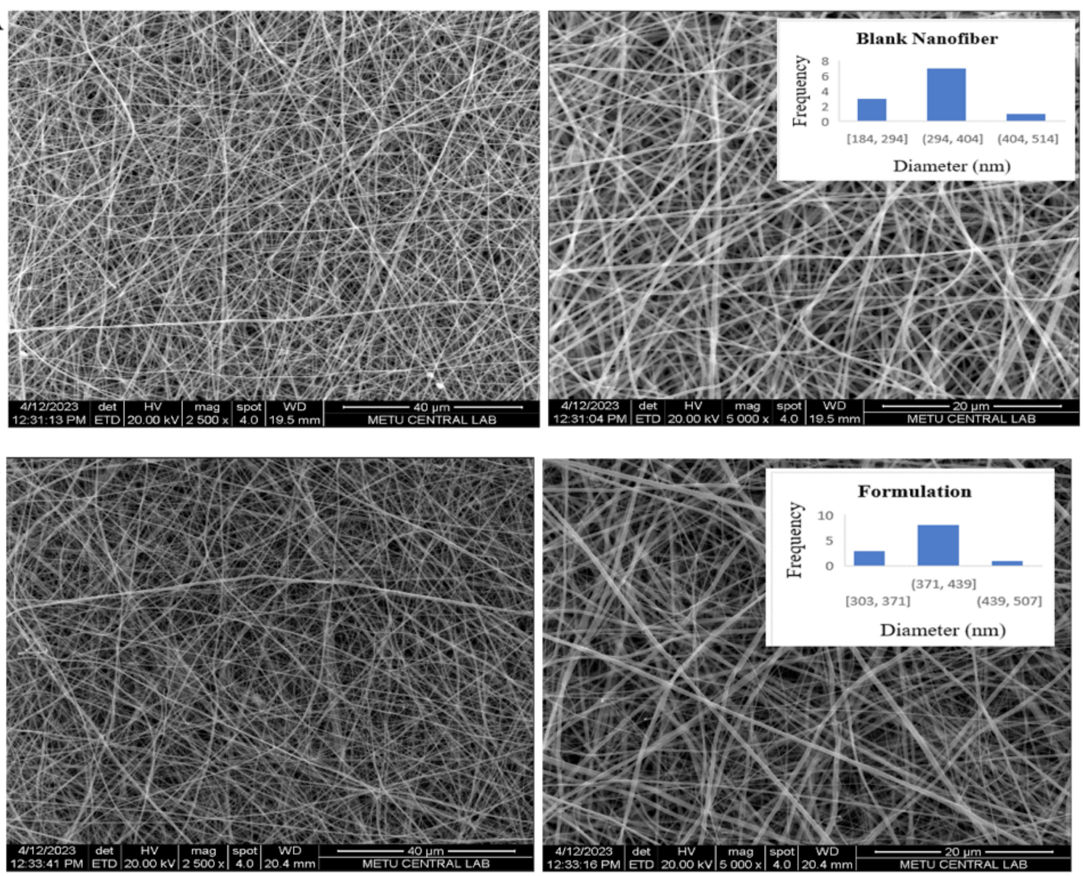


**Figure 3.** SEM images of blank nanofiber (A) and resulting formulation (B) with 2500x and 5000x magnification, respectively.

### Mechanical Properties

After evaluating the elongation of break % results and tensile strength values, Table 3's mechanical properties of the blank nanofiber and resulting formulation were assessed. Also, the results of the mucoadhesion study conducted on the resulting formulation are represented in Table 3. Tensile strength and elongation at break values both decreased after sertraline was added to the formulation. In the study of Tort et al., similar results were found in our study. Values of the fibers made with PVP concentrations' elongation at break (%), varying between 10%, 12.5%, and 15% ranged between 17.68 ± 4.06 - 29.28 ± 2.78, while it decreased to 14.93 ± 4.04 - 19.38 ± 1.85 with the loading of the active substance ornidazole. The tensile strength of the nanofiber without 15% PVP ornidazole was 7.363 ± 0.340 MPa. The tensile strength value of the nanofiber containing 15% PVP-ornidazole, the optimum formulation of which was selected, decreased to 5.12 ± 0.28 MPa.

In comparison to nanofibers without an active ingredient, tensile strength and elongation at break values decreased as the active substance was loaded into the nanofibers. It was determined that the flexibility and interactions between the PVP polymer chains are decreased when the active ingredient is loaded into the fibers. Work of mucoadhesion results ranged from 0.085 ± 0.035 to 0.117 ± 0.064 mJ.cm$^{-2}$. In our study, it was 0.748±0.467 mJ.cm$^{-2}$. It shows higher transmucosal administration (Tort et al., 2019).

**Table 3.** Tensile strength and elongation of break values of nanofibers (n±SD)

| Formulation | Tensile Strength (MPa) | Elongation at Break (%) | Work of mucoadhesion (mJ.cm$^{-2}$) |
|---|---|---|---|
| **Blank nanofiber** | 4.301±0.546 | 35.9±7.46 | - |
| **Formulation** | 0.449±0.284 | 22.6±3.66 | 0.748±0.467 |

**Loading Capacity and Encapsulation Efficiency**

As shown in Table 4, the loading capacity and encapsulation efficiency of the formulation is 4.53±0.31% and 79.61±10.56%, respectively. In the study performed by Ilbasmis-Tamer et al., the results obtained in the formulations prepared with 7.5% PVP are compatible with sertraline nanofibers prepared with PVP at the same concentration (Ilbasmis-Tamer et al., 2022).

**Table 4.** Loading capacity and encapsulation efficiency of nanofiber

| Formulations | Loading Capacity (%) | Encapsulation Efficiency (%) |
|---|---|---|
| **Formulation** | 4.53±0.31 | 79.61±10.56 |

***In vitro* Dissolution Study**

As shown in Figure 4, sertraline release of the formulation occurred 10 minutes after administration, according to the findings of the *in vitro* dissolution study. After 60 minutes, the amount of released sertraline reached 92.63%. The % sertraline release in the results we obtained is similar to the release of sertraline obtained from the buccal film prepared with different polymer mixtures and solvent casting methods in Mahajan A.'s study (Mahajan, 2012). When compared to sertraline tablets prepared with PVP K30, the release of sertraline at the end of 2 hours could not exceed 60%, while the release of sertraline was 92% after 1 hour in our study (Al-Nimry & Jaber, 2017).

Kinetic models were calculated based on the results obtained from the dissolution study. Sertraline is a Biopharmaceutical Classification System (BCS) Class II drug. While evaluating the parameters in determining the kinetic model, the fitness of the obtained release profile to the kinetic release model increases as $r^2_{adj}$ approaches 1, as AIC decreases, and as MSC increases (Tuğcu-Demiröz et al., 2021). The results obtained because of the calculations performed are presented in Table 5. In light of this information, when the kinetic model evaluation criteria are examined, it is seen that the most appropriate kinetic model for sertraline release from the obtained sertraline electrospun nanofiber is Hixson-Crowell.

While a burst release was observed in the range of 12-30 minutes in the dissolution profile of the self-nanoemulsifying drug delivery system (SNEDDS) performed by Nair et al., a regularly increasing release was observed with the change in surface area in accordance with Hixson-Crowell kinetics in nanofiber formulations prepared with PVP K90. (Nair et al., 2022)

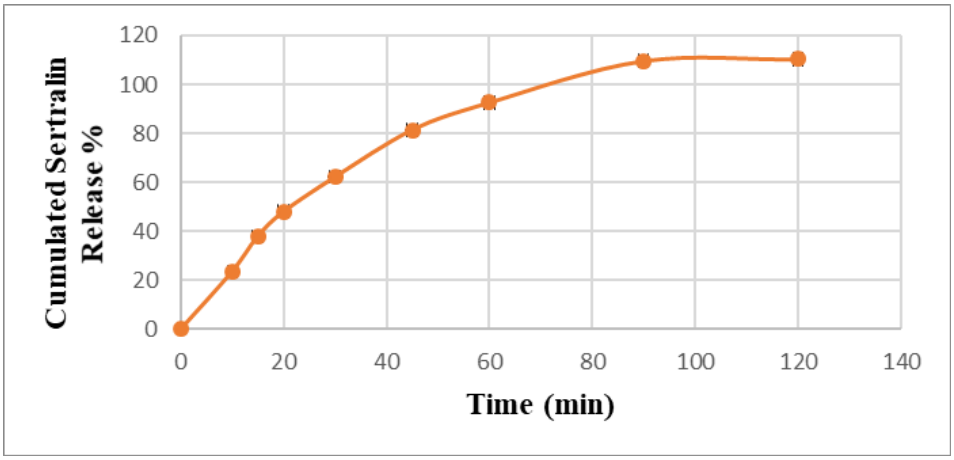


**Figure 4.** *In vitro* dissolution profile of optimum Sertaline nanofiber.

**Table 5.** The adjusted coefficient of determination ($r^2_{adj}$), Akaike information criterion (AIC), and model selection criteria (MSC) for kinetic models were obtained from experimental data via DDsolver

| Kinetic Models | Evaluating Criteria | Formulation |
|---|---|---|
| Zero Order | $r^2_{adj}$ | 0.905004942 |
| | AIC | 46.75619119 |
| | MSC | 1.576997433 |
| First Order | $r^2_{adj}$ | 0.969138373 |
| | AIC | 38.88601213 |
| | MSC | 2.701308728 |
| Higuchi | $r^2_{adj}$ | 0.961374955 |
| | AIC | 40.45672344 |
| | MSC | 2.476921397 |
| Korsmeyer-Peppas | $r^2_{adj}$ | 0.983185199 |
| | AIC | 35.35898273 |
| | MSC | 3.20517007 |
| Hixson-Crowell | $r^2_{adj}$ | 0.998397184 |
| | AIC | 18.18175028 |
| | MSC | 5.659060421 |
| Weibull | $r^2_{adj}$ | 0.99351079 |
| | AIC | 29.13214689 |
| | MSC | 4.094718047 |

## CONCLUSION

In this study, nanofiber strips containing sertraline that can be applied buccally were prepared, especially for use in some schizophrenic patients. According to the polymer characterizations, %5 PVP formulation was decided as the optimum formulation. The percent elongation at break and tensile strength values of 5% PVP-sertraline nanofiber values were found to be appropriate. *In vitro* dissolution studies, sertraline from nanofibers showed Hixson-Crowell dissolution kinetics. In this study, in which buccal electrospun nanofibers containing sertraline were prepared for the first time, it was determined that rapidly disintegrating buccal strips could be obtained successfully. It was concluded that daily doses would be easier to administer in compatible patients such as schizophrenia patients with this formulation. Therefore, it has been demonstrated that the buccal administration of sertraline-loaded nanofibers is a promising drug delivery method for the treatment of schizophrenia.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTION STATEMENT

Formulation development and literature research: KÖ, ESSA. Developing hypotheses, preparing the study text, reviewing the text, statistics, analyzing and interpreting data: SİT, KÖ, ESSA.

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