# PRODUCTION AND CHARACTERIZATION OF NANOFIBER STRUCTURES FOR FAST DISSOLVING TABLET APPLICATIONS

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*"I declare that all the information within this thesis has been gathered and presented in accordance with academic regulations and ethical principles and I have according*
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Jvana ABI

## ABSTRACT

**Master Thesis**

**PRODUCTION AND CHARACTERIZATION OF NANOFIBER STRUCTURES FOR FAST DISSOLVING TABLET APPLICATIONS**

**Jvana ABI**

**Karabük University**
**Institute of Graduate Programs**
**The Department of Biomedical Engineering**

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The pharmaceutical and healthcare industry is heavily dependent on oral treatment to address most health issues. Tablets play an important role, especially for conditions that require treatment in the oral route. The concept of quick-dissolving tablets was introduced to the healthcare industry by the FDA (Food and Drug Administration) in 1998. These tablets do not require water, allowing the medicinal ingredients they contain to dissolve quickly in the mouth by saliva. Rapid-dissolving tablets are designed for a specific group of people who have difficulty swallowing regular tablets, which can be beneficial for conditions such as pediatric patients, patients with mental disorders, chemotherapy patients. These tablets have several advantages in the pharmaceutical sector, can be used anytime and anywhere, can help against motion-induced nausea and can be used during an allergic attack.

The properties possessed by nanofibers, such as flexibility, high porosity and high

surface area to volume ratio, result in a more effective initial phase by enabling faster dissolution and absorption, making them desirable materials for fast dissolving applications. The drug release rate can be modified by modulation of many properties, for example, fiber diameter, morphology and composition. Integrating drugs into nanofibers can be used not only for oral therapies but also in wound healing situations; it can also increase the stability of the drug and improve its bioavailability.

Many polymers have been used for fast dissolving applications, including PVA, PVP, Eudragit and gelatin. PVP nanofibers may be a promising material to overcome the challenges associated with traditional oral drug delivery systems and in the development of fast-dissolving tablets. PVP nanofibers can increase the solubility and dissolution rate of drugs by increasing surface area and wettability. Furthermore, PVP nanofibers can disguise the unpleasant taste of drugs by encapsulating the drug inside the PVP nanofibers, or PVP nanofibers can be loaded with taste disguising agents or flavoring agents, which can be slowly released in the mouth to help disguise the taste of the drug. By controlling their composition, structure and surface chemistry, PVP nanofibers can also be used for targeted drug delivery. By adding PVP and pine pollen to the polymer solution, we can potentially improve the mechanical strength and dissolution rate of the nanofibers, which is important for rapid dissolution applications. Furthermore, depending on the properties of the pine pollen used, it may also contribute to the pharmaceutical properties of pine pollen.

Various techniques have been used for nanofiber production over the years, including electrospinning, Solution Blow Spinning (SBS), Force spinning (Air Jet Spinning), Template Synthesis and Electroblowing (Electrical Blow Spinning, EBS). EBS is a new technique used to produce nanofibers using a wide range of polymers. In this study, we produced nanofibers for fast dissolving tablet applications using EBS method of PVP and pine pollen dust.

In this project, various parameters were studied for the production of modified nanofibers using four polymeric solutions with the same main ingredients but different concentrations. The main ingredients include ethanol, PVP and pine pollen.

The desired properties of the nanofibers produced are: uniform diameter of the fibres, high surface area to volume ratio, suitable morphology, structure uniformity, no droplet formation and suitable mechanical strength.

Both the literature review and experimental studies were discussed in detail. The uniqueness of the study stems from the fact that there is no other study that contains almost no pine pollen.

Various Analyses were performed for nanofiber characterization; SEM (Field Emission Scanning Electron Microscope), FTIR (Fourier Transform Infrared), TGA (Thermogravimetric Analysis), mechanical properties, water contact angle and air permeability analyses were performed within the scope of characterization of the nanofibers produced.

The electroblown nanofibers demonstrated unique characteristics and functionalities. Pine pollen-incorporated PVP nanofibers emerge is a promising candidate for fast dissolving tablets, results showed all fibers exhibit hydrophilicity, and the produced fibers exhibited remarkable antioxidant properties. Furthermore, considering the α-glucosidase activity test results these nanofibers hold potential for applications related diabetes.

**Key Word** **:** Nanofibers, Polyvinylpyrrolidone, Pine Pollen, Electroblowing.

**Science Code** **:** 92503

# ÖZET

**Yüksek Lisans Tezi**

## HIZLI EMİLEBİLEN TABLET UYGULAMALARI İÇİN NANOLİF YAPILARININ ÜRETİMİ VE KARAKTERİZASYONU

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Farmasötik ve sağlık sektörü, sağlık sorunlarının çoğunu ele almak için ağız yoluyla tedaviye büyük ölçüde bağımlıdır. Özellikle oral yolda tedavi gerektiren durumlar için tabletler önemli bir rol oynamaktadır. Hızlı çözülen tabletlerin konsepti, FDA (Gıda ve İlaç İdaresi) tarafından 1998 yılında sağlık sektörüne tanıtıldı. Bu tabletler, içerdikleri tıbbi malzemelerin ağızda tükürük tarafından hızla çözülmesini sağlayarak, su gerektirmez. Hızlı çözülen tabletler, normal tabletleri yutmakta zorlanan belirli bir grup insan için tasarlanmıştır, bu da pediatrik hastalar, zihinsel rahatsızlığı olan hastalar, kemoterapi hastaları gibi durumlar için faydalı bir alternatif sunabilir. Bu tabletlerin farmasötik sektörde çeşitli avantajları vardır, her zaman ve her yerde kullanılabilir, hareketle indüklenen bulantılara karşı yardımcı olabilir ve alerjik saldırı sırasında kullanılabileceği bilinmektedir.

Nanofiberlerin sahip olduğu esneklik, yüksek gözeneklilik ve yüksek yüzey alanı

hacim oranı gibi özellikler, daha hızlı çözünme ve emilim sağlayarak daha etkili bir başlangıç aşamasına neden olur, bu da hızlı çözülen uygulamalar için arzu edilen malzemeler yapar. İlaç salım hızı, örneğin fiber çapı, morfoloji ve kompozisyon gibi birçok özelliğin modülasyonu ile değiştirilebilir. İlaçların nanofiberlere entegre edilmesi, sadece oral tedaviler için değil, aynı zamanda yara iyileşme durumlarında da kullanılabilir; ayrıca ilacın stabilitesini artırabilir ve biyo-yararlanımını geliştirebilir.

Hızlı çözülen uygulamalar için birçok polimer kullanılmıştır, bunlar arasında PVA, PVP, Eudragit ve jelatin bulunmaktadır. PVP nanolifler, geleneksel oral ilaç dağıtım sistemleriyle ilişkili zorlukların üstesinden gelmek ve hızlı çözünen tabletlerin geliştirilmesinde umut vadeden bir malzemedir. PVP nanolifler, yüzey alanını ve ıslanabilirliği artırarak ilaçların çözünürlüğünü ve çözünme hızını artırabilir. Ayrıca, PVP nanolifler, ilacı PVP nanoliflerinin içine kapsülleyerek hoş olmayan tatlarını gizlemek mümkündür veya PVP nanolifleri tat gizleme maddeleri veya aroma maddeleriyle yüklenebilir ve bu maddeler ağızda yavaşça salınarak ilacın tadını gizlemeye destek temin edebilir. PVP nanolifleri, bileşimlerini, yapılarını ve yüzey kimyasını kontrol ederek, hedefe yönelik ilaç dağıtımı için de uygundur.

Çam poleni çeşitli sağlık yararları nedeniyle kullanıldı. Çam poleni polimer çözeltisine ekleyerek, nanoliflerin mekanik dayanıklılığını ve çözünme hızını potansiyel olarak artırabilmesi düşünüldü, bu da hızlı çözünme uygulamaları için önem arz etmektedir. Ayrıca, kullanılan çam poleni özelliklerine bağlı olarak, çam poleninin farmasötik özelliklerine de katkıda bulunabilir.

Yıllar boyunca nanofiber üretimi için çeşitli teknikler kullanılmıştır, bunlar arasında elektrospinning, Solution Blow Spinning (SBS), Force spinning (Air Jet Spinning), Template Synthesis ve Elektroblowing (Electrical Blow Spinning, EBS) bulunmaktadır. EBS, geniş bir polimer yelpazesi kullanarak nanofiberler üretmek için kullanılan yeni bir tekniktir. Bu çalışmada, PVP ve çam polen'nin EBS yöntemi kullanılarak hızlı çözülen tablet uygulamaları için nanofiberler üretilmesi gerçekleştirildi.

Bu projede, aynı ana içeriklere sahip ancak farklı konsantrasyonlara sahip dört polimerik çözüm kullanılarak modifiye nanofiberlerin üretimi için çeşitli parametreler incelenmiştir. Temel içerikler arasında etanol, PVP ve çam poleni bulunmaktadır. Üretilen nanofiberlerin istenen özellikleri şunlardır: fiberlerin çapının düzenli olması, yüksek yüzey alanı hacim oranı, uygun morfoloji, yapı bütünlüğü, damla oluşmaması ve uygun mekanik dayanıklılık.

Bu tezde, hem literatür taraması hem de deneysel çalışmalar detaylı bir şekilde tartışıldı. Çalışmanın benzersizliği, neredeyse hiç çam poleni içermeyen başka bir çalışma olmamasından kaynaklanmaktadır.

Nanofiber Karakterizasyonu için çeşitli analizler gerçekleştirildi; üretilen nanoliflerin karakterizasyonu kapsamında SEM (Field Emission Scanning Electron Microscope), FTIR (Fourier Dönüşümlü Kızılötesi), TGA (Termogravimetrik Analiz), mekanik özellikler, su temas açısı ve hava geçirgenliği analizleri yapıldı.

Üretilen nanolifler benzersiz özellikler ve işlevler sergilemiştir. Çam poleni katkılı PVP nanolifler hızlı çözünen tabletler için umut verici bir aday olarak ortaya çıkmıştır, sonuçlar tüm liflerin hidrofiliklik sergilediğini ve üretilen liflerin dikkate değer antioksidan özellikler sergilediğini göstermiştir. Ayrıca, α-glukozidaz aktivitesi test sonuçları göz önüne alındığında, bu nanolifler diyabetle ilgili uygulamalar için potansiyel taşımaktadır.

**Anahtar Sözcükler :** Nanolif, Elektrik Destekli Çözelti Üfleme, Polivinilpirolidon, Çam poleni.

**Bilim Kodu :** 92503

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## SYMBOLS AND ABBREVIATIONS INDEXD

### SYMBOLS

mg GAE/g: Milligrams of Gallic Acid Equivalent per gram.

μM TE/g: Micromoles of Trolox Equivalent per gram

nm : Nanometers

KN : Kilonewtons

NM : Nanometers

mm/s : Millimeters per second

°C : Degrees Celsius

MPa : Megapascal

### ABBREVIATIONS

PVP : Polyvinylpyrrolidone

CMC : Carboxymethyl Cellulose

PVA : Polyvinyl Alcohol

HPC : Hydroxypropyl cellulose

PP : Pine Pollen

SBS : Solution Blow Spinning

EBS : Electroblowing

SEM : Scanning Electron Microscope

FTIR : Fourier Transformed Infrared

TGA : Thermogravimetric Analysis

DPPH : 2,2-diphenyl-1-picrylhydrazyl

ABTS : 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid))

# PART 1

## INTRODUCTION

Pharmaceutical and health sector depends greatly on the oral route to address major of health problems, tablets are considered to have a great role in treatments that depends on the oral route owing to its uncomplicated manufacturing, self-administration and many other benefits [1]. The concept of fast-dissolving tablets was first introduced into the health sector in 1998 by the FDA (Food and Drug Administration) [1]. These tablets that contain the needed medical materials can be dissolved rapidly within seconds in the mouth by the saliva with no water needed [1]. The idea of the fast-dissolving tablets was established to overcome problems faces a certain group of people that suffer from difficulties swallowing normal tablets, patients like pediatric, patients with mental illness, and chemotherapy patients. It can also be beneficial for patients that are uncooperative [2]. Fast-dissolving tablets have many beneficials that made it desirable in the pharmaceutical sector, it can be used anytime and anywhere, it can help during motion-induced nausea, and it can be used during allergic attacks. It can eliminate the necessity of water [1].

The properties possessed by nanofibers such as flexibility, high porosity, and high surface area to volume ratio that leads to faster dissolution and absorption rates which cause a better onset of action, made it desirable materials for fast dissolving applications, we can also relieve the unfavorable granular sensation associated to taking the medicine with a more pleasant taste in the oral cavity [3,4]. The drug release rate can be modified by modulating many properties for example fibers diameter, morphology and the composition.

Drug incorporation into nanofibers can be used not only for oral treatments but also can be used for wound healing cases, additionally it can enhance drug stability and the bioavailability.

Many polymers were used in the production of nanofibers for fast dissolving applications, poly (vinyl alcohol) (PVA), polyvinylpyrrolidone (PVP), Eudragit, and gelatin are some of the used polymers [3]. PVP is a polymeric material that have been used in the production of pharmaceutical tablets, it is known for its ability to improve the solubility and the distribution of the drug components in the tablets which leads to better effectiveness of the drug, and better absorption by the body. Also, PVP which is a hydrophilic polymer with a perfect water solubility can be described as a fast-dissolving material. This made PVP a desirable polymer for the creation of fast dissolving nanofibers.

Pine pollen (pp), a natural substance with many bioactive ingredients and therapeutic advantages can be a proper material to be involved in the nanofibers production along with PVP for our pharmaceutical purpose. PP contain terpenoids that can help with the flavor of the pharmaceutical tablets, phenolic which is known for its antioxidant properties, also has potentials to be an anti-inflammatory agent, and flavonoids that are known for its antioxidant, antimicrobial, and anti-inflammatory properties [5].

Different techniques were used through the years for nanofibers production, each has its unique properties as well as its limitations Based on the application, the properties desired from the nanofibers can be affected by the used polymers, materials, a proper fabricating technique. Electrospinning, Solution Blow Spinning (SBS), Force spinning (Air Jet Spinning), Template Synthesis, and Electroblowing (Electrical Blow Spinning, EBS) are examples for the techniques used in nanofibers production [4].

EBS is a novel technique used to produce non-woven nanofibers using a vast range of polymers [6]. This method produces fibers with high surface area-to-volume ratio

which is beneficial in various purposes such as drug delivery systems, tissue engineering, and filtration.

In this project, our purpose is to create nanofibers from PVP polymer along with PP as an agent using EBS method for fast dissolving tablet applications. Different polymeric solutions with different ingredients were used in order to determine the proper ratios to be used in the production of the desired nanofibers. In this work a total of four solutions with different percentages of PVP and PP were made, different parameters were examined while producing the modified nanofibers, thereafter the characteristics of the produced fibers were examined.

The desired properties of the produced nanofibers are as follows; uniform diameter of the fibers, high surface area-to-volume ratio, proper morphology with structural integrity, no droplets formation, and avoiding unsuitable mechanical strength.

In this thesis both literature review and experimental studies are discussed. Details about nanofibers, PVP, PP, experimental design, and the results along with the discussions is discussed in the next chapters. It is important to state that this study is unique as there is almost no study that involves pine pollen in nanofibers production.

## PART 2

## NANOFIBERS

Nanofibers, characterized by their slender dimensions in the nanometer range (1 nanometer = $10^{-9}$ meters) and flexible properties, are widely recognized within scientific literature. The distinguishing characteristics of nanofibers are their exceptional surface area-to-volume ratio, which arises due to their nanoscale dimensions. Typically possessing small diameters between 100–500 nm, the multiplicity of nanofibers when aggregated leads to a substantial increase in the collective surface area. This augmented surface area relative to the volume serves to enhance interactions with diverse substances, rendering nanofibers suitable for a myriad of applications. The remarkable structural and mechanical attributes of nanofibers further contribute to their prominence in scientific research. Additionally, nanofibrous materials exhibit a significant presence of pores, enhancing their functionality in specific applications. The fabrication of nanofibrous structures can be achieved using a variety of materials and techniques, providing opportunities for customization and optimization for intended uses. As a result, nanofibers obtain extensive utility in a broad range of fields including tissue engineering, wound dressing, sensor technology, membrane design, drug delivery systems, and filtration processes [7].

Presently nanofibers can be used for supercapacitors, fuel cells, solar cells, and batteries. Also, these fibers are beneficial for water purification, air filtration, and blood purification [8].

In the realm of biomedical applications, nanotechnology, encompassing the study of nanofibers, has been the subject of extensive research. The purpose of this research is to leverage the distinctive biological, physical, and chemical characteristics of nanofibers, with a particular emphasis on their application in drug delivery systems.

The inherent attributes of nanofibers, which encompass biodegradability, effective cellular uptake, biocompatibility, and controlled content release, have garnered substantial interest and engendered significant promises within the field of pharmaceutical applications and drug delivery systems [9].

The selection of materials for nanofiber formation is a pivotal decision contingent on the desired characteristics. This choice exerts a substantial influence on the properties of the resultant nanofiber networks. Factors under consideration encompass attributes like biocompatibility, electrical conductivity, and mechanical strength. Polymers, encompassing both natural and synthetic varieties, stand as a preeminent choice in the extensive production of diverse nanofibers. Polymeric nanofibers, irrespective of their natural or synthetic origin, exhibit exceptional and auspicious attributes within the realm of medical research. These fibers with its substantial surface area characteristics can facilitate material transport within nano-systems. Additionally, they are characterized by high packing efficiency, notable porosity, ease of manipulation and operation, and a significant degree of thermal and chemical stability [9].

The suitable polymer shall be introduced into an appropriate solvent, contingent upon the specific attributes sought. Subsequently, this resultant polymeric solution will be employed for the generation of nanofibers. Various factors warrant consideration during the production of nanofibers. These factors encompass elements related to the polymeric solution and facets pertaining to the fabrication methodology [9].

Table 2.1. Some polymeric solution parameters [10].

| **solution parameters** | **Effects on the produced fibers** |
|---|---|
| Molecular weight of the used polymer | (1) High molecular weight leads to formation of uniform beadless nanofibers.<br>(2) Low molecular weight requires higher concentrations. |
| Polymer concentration | (1) High concentrations leads to increasing in nanofiber diameters.<br>(2) Low concentrations results in bead formation. |
| Viscosity | (1) High viscosity leads to increasing in the fibers diameters and promote fibers stability .<br>(2) Low viscosity procure to bead formation. |

## 2.1. FABRICATION METHODS FOR NANOFIBERS

Nanofiber fabrication methods exhibit a classification dichotomy, which can be exemplified by the differentiation between bottom-up and top-down approaches. These methods may also be categorized into chemical, physical, and biological approaches. Furthermore, the fabrication techniques fall into two main categories: spinning and non-spinning methods [8].

Physical processes in nanofiber fabrication typically leverage thermal or electrical energy, mechanical pressure, and high-energy radiations to induce condensation, melting, or evaporation of the materials employed. Examples of physical processes include laser ablation, physical vapor deposition (PVD), milling, grinding, and various spinning techniques. Chemical methods in nanofiber fabrication involve the assembly of small entities such as atoms, ions, or molecules to form extended one-dimensional nanofibers, as opposed to isolated nanoparticles. This is characterized as

a bottom-up approach. Instances of chemical processes encompass sonochemical synthesis, template-assisted synthesis, electrochemical deposition, sol–gel methods, microwave synthesis, chemical vapor deposition (CVD), and hydrothermal techniques. In response to the limitations associated with physical and chemical methods, research has delved into biological fabrication methods. These environmentally friendly techniques produce cellulose nanowebs by deriving them from diverse lignocellulosic fibers through enzymatic and bacterial cellulose treatment. Notable examples of biological processes include enzymatic hydrolysis of wood pulp and bacterial cellulose synthesis. Furthermore, spinning techniques, rooted in traditional physical fabrication methods, are employed to generate fibers from polymeric solutions. These techniques can be integrated with the majority of the aforementioned physical and chemical methods to enhance the nanofiber fabrication process, resulting in nanofibers with improved characteristics. Spinning techniques can be further subdivided into electrospinning, which utilizes electrostatic forces, and non-electrospinning, employing alternative forces such as pressurized air, gravitational forces, and centrifugal forces [8].

Nanofiber spinning techniques both electro and non-electro spinning techniques are listed in Table 2.2.

Table 2.2. Nanofiber spinning techniques [8].

| **Electro spinning techniques** | **Non-electro spinning techniques** |
|---|---|
| Needless electrospinning | Air-jet spinning |
| Multiple-jet electrospinning | Centrifugal spinning |
| Bubble electrospinning | Drawing technique |
| Electroblowing | İslands-in-sea spinning |
| Solvent-free electrospinning | Flash-spinning |
| Bundling electrospinning. | Laser spinning |
| Charge injection electrospinning | Wet spinning |

### 2.1.1. Electrospinning

The electrospinning technique employs needleless as well as multi-needle spinneret systems and is routinely employed for the fabrication of fibers ranging in dimensions from the micro to the nano scale, finding diverse applications in both scientific research and various industrial sectors. The inception of this method traces back to the period between 1861 and 1903 when Morton and Cooley devised the electrohydrodynamic spray method, a means of dispersing fluids via electrostatic forces. Subsequently, Formhals harnessed this electrostatic tool to electrospin fibers. It wasn't until the 1990s that researchers and scientists began to take a heightened interest in the electrospinning technique. Over the years, spanning from 1934 to 1944 and 1855 to 1944, a multitude of patents were filed for electrospinning devices intended for the production of polymeric fibers [11].

The electrospinning process entails subjecting a polymeric solution to high-voltage electricity, causing it to be ejected from a nozzle, thereby forming a jet that proceeds to dry and subsequently deposits on a collector. Numerous factors exert a significant influence on this method, playing pivotal roles in shaping the characteristics of the resulting nanowebs. These influencing factors encompass properties of the polymer solution, including molecular weight, polymer concentration, and solution viscosity. Additionally, the attributes of the electrospinning device itself and the environmental conditions, such as humidity, temperature, and air flow within the workspace, contribute to the method's overall efficacy and the properties of the generated nanofibers [11].

Device properties that affect the resulting nanowebs.:

1. Application of the electrical potential.
2. The inner orifice diameter of the spindle.
3. Flow rate of the polymerics melt.
4. Spinneret - collector distance.
5. Needle gauge.
6. The movement and the size of the collector [11].

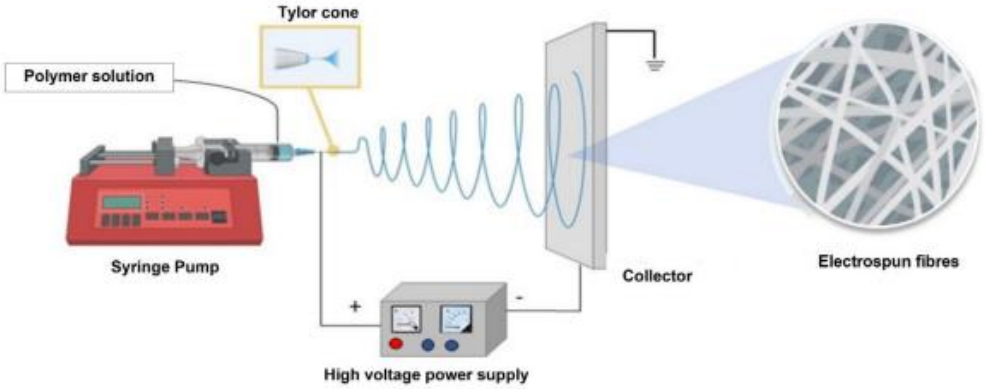



Figure 2.1. A general scheme of electrospinning setup [6].

### 2.1.2. Solution blowing

The SBS method, also referred to as the melt-blowing method, is an evolving spinning process characterized by a concentric nozzle arrangement that combines two parallel streams of polymeric melt encircled by a flow of gas to generate an expansive jet. At the nozzle's terminus, the high-pressure gas transitions to atmospheric pressure, inducing a shearing force at the gas-solution interface. This shearing force effectively counteracts the surface tension of the polymer, expelling the solution stream from the nozzle in alignment with the gas stream. The SBS method is favored primarily for its safety and ease of operation. Furthermore, it is renowned for its exceptional scalability and deposition rate that is outpacing electrospinning by a magnitude of tenfold [6].

The demand for nanofibers produced via the SBS method, especially for biomedical applications, has witnessed a dramatic upsurge owing to its capacity for the rapid generation of biological scaffolds and the in-situ fabrication of tailored materials. Despite its numerous advantages, researchers and scientists are actively addressing certain challenges inherent to the SBS method. These challenges encompass issues like nozzle clogging, unregulated deposition of the fabricated nanowebs, and jet instability. For instance, Li et al. observed the occurrence of bead formation in alumina nanofibers produced via the SBS method, attributed to factors such as jet instability and nozzle tip blockage during the spinning process. Additionally, Ray et

al. noted that the length of the nozzle protrusion obstructed airflow, leading to disturbances in the resulting jet and disruptions in nanofiber continuity. It has been recognized that the design of the nozzle can significantly impact the morphological characteristics of the generated nanowebs. In a study conducted by Han et al., aimed at elucidating the influence of nozzle diameter and needle protrusion length on the diameter of nanofibers produced from chitosan and polyethylene oxide (PEO), it was established that a larger internal nozzle orifice yields nanofibers of greater diameter, while a very small orifice produces nanofibers of finer diameter [6].

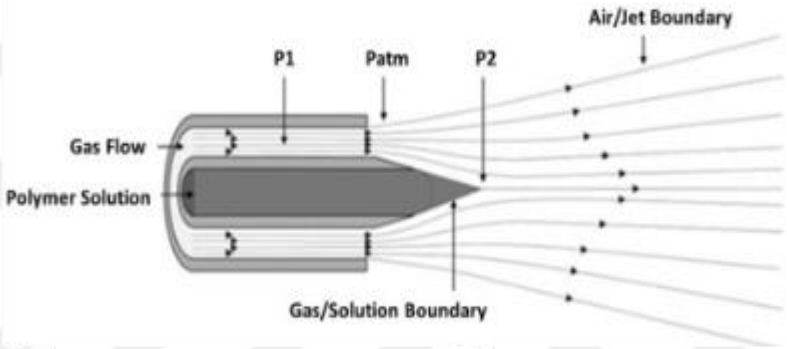



Figure 2.2. SBS working principle [6].

### 2.1.3. Electroblowing

Electroblowing (solution blown spinning) represent one of the most extensively investigated technique within the realm of spinning processes. Research has indicated that electrospun nanofibers tend to exhibit larger diameters while having a smaller surface area. Conversely, nanofibers produced via the solution blown spinning (SBS) method demonstrate higher density and productivity, EBS can be described as combining driving forces. of both electrospinning and solution blowing [6].

The concept of merging electric fields with pressurized air forces first surfaced in 2004 when Um et al. introduced the notion of creating high molecular weight hyaluronic acid (HA) through an electric-field-assisted air blowing spinning mechanism. This innovative approach, known as Electroblowing (EBS), involves the

concurrent application of electric fields and high-pressure gas forces. Electroblowing has the potential to overcome the limitations associated with SBS, which includes issues such as solution accumulation, spinneret blockage, and jet instability. Moreover, it offers a solution to the constraints of electrospinning, notably its limitations in terms of production rates [6].

The Electroblowing (EBS) mechanism comprises the following components:

1. A syringe pump.
2. A Solution Blown Spinning (SBS) concentric nozzle.
3. A source of compressed air.
4. An electrical field.
5. A rotating drum collector [6].

In this mechanism, pressurized airflow and an electrical field are applied to the polymeric solution as it is expelled from the spinneret tip, resulting in the formation of nanowebs with a wide range of diameters, spanning from 10 μm down to 68 nm. The primary force in close proximity to the nozzle's tip is the pressurized airflow. As the distance between the nozzle and the collector increases, the spinning process becomes more stable due to the dominance of electrostatic repulsive force. This mechanism is characterized by a notably high production rate, rapid spinning speed, and exceptional solution jet stability. The resulting nanofibers exhibit homogeneous distribution and precise diameters. Furthermore, the morphology of the fibers are more controlled and evenly distributed [6].

Shi et al., have made a study to compare SBS and EBS, the results showed that EBS fibers were finer and more uniform [12].

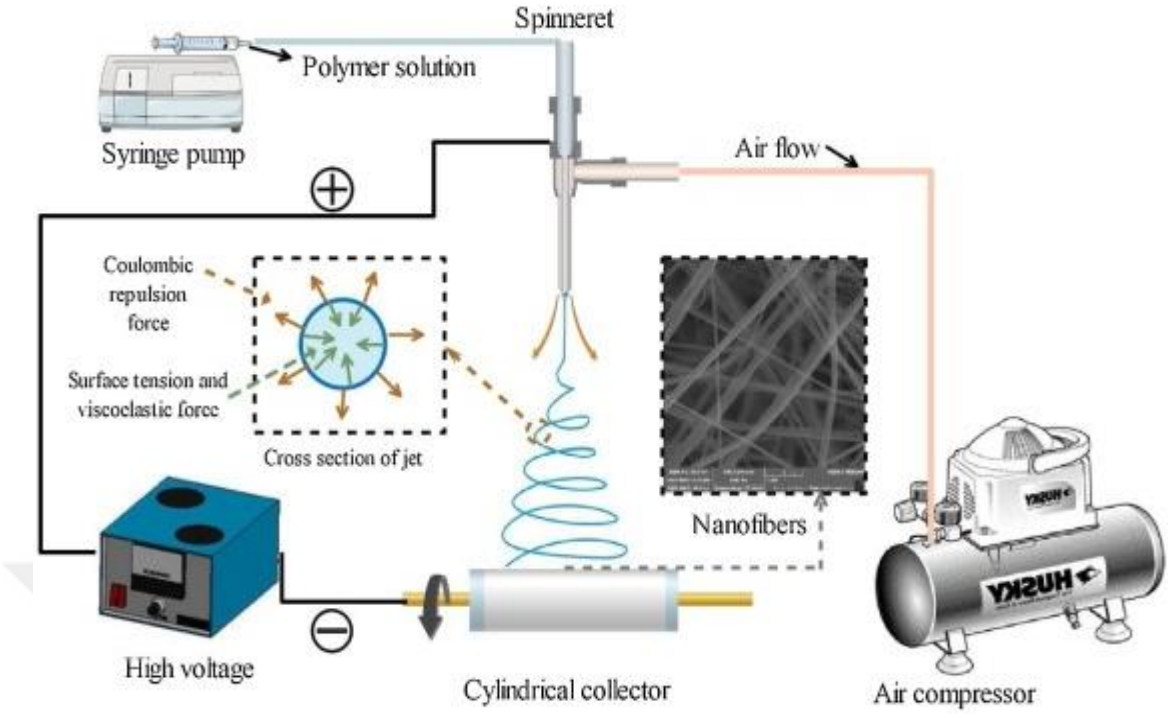



Figure 2.3. A general scheme of EBS [6].

Table 2.3. Different factors that affect the morphological structure and the diameters of the EBS nanofibers [6].

| **Parameters** | **Affects** |
|---|---|
| Parameters related to the method | Feeding rate<br>Voltage<br>Air pressure<br>Working distance |
| Ambient parameters | Temperature<br>Humidity |
| Polymer solution | Concentration |

Polymeric melts with high concentrations, which correspond to increased viscosity, tend to yield nanofibers with larger diameters. The feeding rate, a critical parameter associated with the method, plays a significant role. Excessive flow rates can lead to issues such as solution leakage, nozzle blockage, and the production of nanofibers

with larger diameters. Similarly, elevating the applied voltage can result in the generation of continuous, fine, and uniformly distributed nanofibers. Higher air pressure tends to produce nanofibers with small diameters and higher production yields. The working distance, or the distance between the spinneret and collector, also influences the process. Increasing the working distance enhances the likelihood of solvent evaporation, ultimately leading to the formation of nanofibers with smaller diameters [6].

It's imperative to consider the impact of ambient factors, such as humidity and room temperature. Elevated humidity levels can cause rapid solidification of nanofibers, and results in small diameters. additionally, an increase in ambient temperature fosters great nanofiber continuity, enhanced flexibility, and a narrower diameter distribution [6].

## 2.2. COMPARISION BETWEEN ELECTROSPINNING, SOLUTION BLOWING, ELECTROBLOWING

In light of the information presented in the preceding section, a comparative analysis of these three methods can offer a comprehensive understanding:

**Electrospinning Process:** This method entails the application of an electric field generated by a high-voltage power supply. The electric field operates between a syringe containing polymeric melt and the collector, facilitating the formation of continuous nanofibers. These nanofibers are known for their uniformity and exhibit diameters ranging from a few nanometers to several micrometers. Electrospinning finds suitability in a diverse range of applications, including drug delivery, tissue engineering, sensors, and filtration.

**Solution Blowing:** Solution blowing operates by utilizing high-pressure gas to create nanofibers, devoid of any involvement of electrical forces. The resultant nanofibers typically possess larger diameters and a varied structural profile when compared to electrospun fibers. This method is well-suited for applications such as thermal insulation and air filtration.

**Electroblowing:** Electroblowing is a hybrid method that combines elements of both electrospinning and solution blowing techniques. This approach leverages both electrical and gas forces to produce nanofibers with significantly smaller diameters. Electroblowing, as a result of this dual influence, offers a unique advantage in achieving diversity in fiber properties.

Each of these methods exhibits distinctive features, rendering them suitable for various applications. Electrospinning excels in the production of fine, uniform mats. In contrast, solution blowing stands out for its capability to yield large-scale outputs and larger mats. Electroblowing, by combining features from both methods, offers a versatile approach that can be tailored to specific requirements for fiber properties. Advantages and disadvantages of each method are listed in Table 2.3 below.

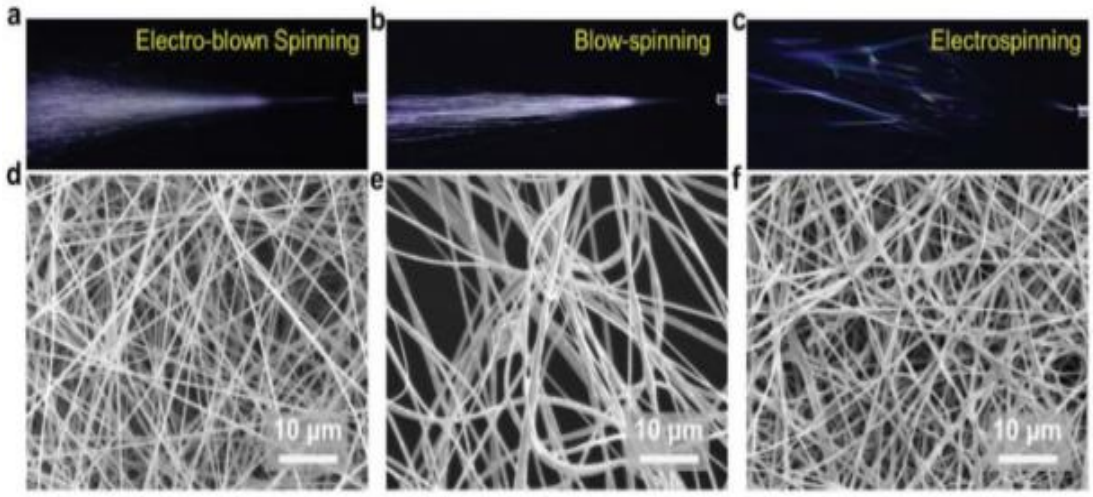



Figure 2.4. Snapshots of solution jet and SEM image of electro-blown spinning (a and d), blow spinning (b and e), and electrospinning (c and f) [6].

Table 2.4. Advantages and disadvantages of the Electrospinning, SBS, and EBS processes [6].

| **Techniques** | **Advantages** | **Disadvantages** |
|---|---|---|
| Electrospinning | Cost-effective<br>Simple operation | High voltage danger<br>Limitation of the conductive polymers |
| Solution blowing | Large-scale production<br>Safty<br>Wide range of materials<br>Appropriate for industrial prospect | Jet instability and nozzle clogging<br>Uneven distribution of nanofibers<br>Formation of bundles at high air flow |
| Electroblowing | Fine and uniform nanofibers<br>Stable solution jet<br>Suitable for highly viscous polymers | Control multiple parameters simultaneously |

In this thesis electroblowing (EBS) is the fabrication methode that used to fabricate the nanofibers.

## PART 3

## FAST DISSOLVING TABLETS

Over the course of several years, the oral route has consistently emerged as the preferred method for drug administration. Patients often choose the oral medications, such as tablets, due to the simplicity of their production, ease of self-administration, and a multitude of other advantages [1].

However, this method has encountered various challenges and issues that affect a substantial number of patients. Complaints regarding oral tablets have been particularly prevalent among pediatric, geriatric, mentally ill, vomiting-prone, and dysphagia-afflicted patients. These challenges can lead to difficulties in adhering to prescribed medication regimens, resulting in a noteworthy rate of non-compliance [2].

In an effort to address these challenges, fast-dissolving tablets were introduced to the medical field in 1998, gaining approval from the FDA. These tablets possess the unique ability to rapidly disintegrate and dissolve upon exposure to saliva in the oral cavity, obviating the need for water [1]. Additionally, fast-dissolving films were developed as a promising buccal delivery method, recognized as an ideal approach for drug delivery. It is well-documented that, following buccal and sublingual administration, drug substances are swiftly absorbed by the reticulated vein, thereby entering the systemic circulation [13]. Moreover, some drugs suffer from poor solubility, which can hinder their absorption. In addressing this limitation, nanofibers have been employed as carriers to enhance solubility and subsequently improve bioavailability [3,14].

Ideal features of fast dissolving tablets:

1. Do not need water to dissolve.
2. Disintegrates rapidly within seconds when placed in mouth.
3. Low sensitivity to environmental conditions such as humidity and temperature.
4. Easy to transmit.
5. Rapid dissolution and absorption rates.
6. By nature of being unit dosage forms they must supply accurate dosing.
7. Manufactured using low-cost equipment.
8. Should maintain its hardness [15].

### 3.1. NANOFIBERS FOR FAST DISSOLVING TABLETS

A common limitation related to the bioavailability of drugs pertains to poor water solubility. To overcome this challenge, scientists have pursued a range of strategies aimed at enhancing the dissolution rate of compounds that exhibit low solubility in water, particularly for oral administration. These strategies include the incorporation of agents such as wetting and surfactant agents, dispersion of amorphous solids, and integration with hydrophilic polymers [14].

In the case of immediate-release tablets, the active pharmaceutical ingredient is often combined with substances that can ameliorate both dissolution and bioavailability. These substances may encompass polyvinylpyrrolidone (PVP), lactose, hydroxypropyl methylcellulose (HPMC), polyethylene glycol, and citric acid. The electrospun nanofibers have garnered considerable attention in this context due to their exceptional properties. In addition to their high surface area-to-volume ratio and porous structure, these nanofibers exhibit remarkable drug-loading capabilities [14].

Electrospun nanofibers have proven instrumental in addressing the issue of low drug dissolution rates, especially for poorly water-soluble drugs. Numerous studies have explored the use of electrospun polymeric nanofibers to encapsulate drugs with low solubility, including meloxicam, ondansetron, nebivolol, acetylsalicylic acid,

paracetamol, ketoprofen, carvedilol, caffeine, and ibuprofen. Furthermore, investigations have demonstrated the potential of polymers such as Polyvinylpyrrolidone (PVP) and Polyvinyl alcohol (PVA) in the fabrication of nanofibers designed for drug delivery systems. These studies have underscored the dissolution performance and high drug-loading capacity of these nanofibers [14].

The novelty introduced in this manuscript pertains to the innovative application of drug-loaded electrospun nanofibers as a primary material for tablet manufacturing. Leveraging the distinctive properties of drug-loaded nanofibers, it has been demonstrated that they offer enhanced drug release characteristics compared to free drugs, particularly in the case of drugs with low solubility. The ability to grind and compress these nanofibers to create tablets while preserving the desired drug dissolution profile presents a noteworthy and advantageous alternative approach for the production of pharmaceutical oral dosage forms [14].

The aim of the project is to benefit the unique properties of nanofibers that show enhanced drug release even for the low soluble drugs to be alternative for oral pharmaceutical substances productions.

### 3.2. POLYMERS USED FOR FAST DISSOLVING TABLETS

Various types of polymers find applications in the formulation of fast-dissolving products. A range of polymers can be employed individually or in combination to achieve specific desired properties. Examples of polymers suitable for these applications encompass cellulose, pullulan, methylmethacrylate copolymer, guar gum, tragacanth gum, acacia gum, polyvinylpyrrolidone, hydroxypropylcellulose, hydroxyethylcellulose, carboxymethylcellulose, polyvinyl alcohol, hydroxypropylmethyl cellulose, gelatin, cellulose derivatives, xanthan gum, hypromellose, and sodium alginate [16].

Kulkarni et al. (2010) conducted an exploration of various polymers for the development of oral fast-dissolving strips. Their study encompassed the utilization of multiple polymers, including polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA),

pullalan, and gelatin, in the formulation of fast-dissolving buccal films, pullalan showed the best results to be used for fast-dissolving buccal films [16].

Table 3.1. Properties of some polymers in fast dissolving tablets applications.

| **Polymer** | **Property** |
|---|---|
| Polyvinyl alcohol (PVA) | produce strong films with enhanced drug stability. |
| Polyvinylpyrrolidone (PVP) | Enhances drug dissolution, and enhanced bioavailability. |
| Polyethylene oxide (PEO) | Enhances solubility, and enhances bioavailability. |
| Methyl cellulose | Controlled release, enhances stability. |
| Pullulan | Biocompatible, usable in oral drug delivery applications. |
| Xanthan gum | Enhances film formation, and provides viscosity, |

### 3.3. INTRODUCTION TO PVP, PROPERTIES AND USES

Polyvinylpyrrolidone (PVP) is a synthetic polymer characterized by its biocompatibility and non-toxic nature. This polymer is derived from the N-vinylpyrrolidone monomer and is formed through the repetition of vinylpyrrolidone monomers. Its molecular weight can range from low to high, impacting properties like viscosity and other characteristics. PVP is soluble not only in water and alcohol but also in various organic solvents, making it versatile for numerous applications. It is recognized for its safety profile, lacking toxic or irritating effects, and finds application in a multitude of industries, including food, pharmaceuticals, and cosmetics [17].

PVP's binding and film-forming properties have made it valuable in the cosmetic sector, where it is employed in hair sprays, gels, skincare products as a stabilizing agent, and viscosity enhancer. Furthermore, PVP extends its utility to textiles,

detergents, adhesives, and food processing. Its biocompatibility, non-toxicity, hydrophilicity, and antibacterial properties render it an ideal choice for applications in biomedicine and the pharmaceutical industry. PVP is employed as an adhesive in various medical tablets and is known for its rapid absorption within the body when administered orally [17].

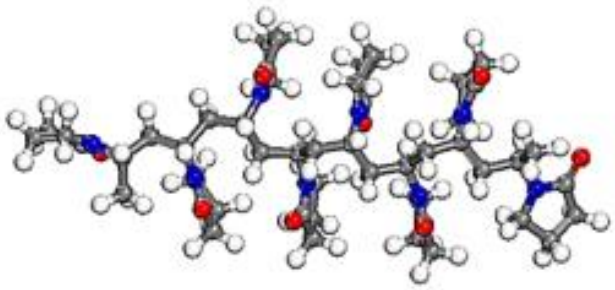


Figure 3.1. Optimized structures of PVP based on DFT-D in Material Studio 2017 [17].

## 3.2. INTRODUCTION TO PINE POLLEN, PROPERTIES AND USES

This thesis focuses on the utilization of pine pollen (PP) as the chosen agent for the production of polyvinylpyrrolidone (PVP) nanofibers. Pine pollen, widely employed in traditional Chinese medicine and recognized for its health potentials and bioactive compounds, exhibits an array of notable properties. These properties encompass antioxidant, anti-inflammatory, immunomodulatory, regulation of lipid and glucose metabolism, anticancer, antimicrobial, antiviral, anti-aging, and diverse other biological features. Consequently, pine pollen finds applicability in various areas, ranging from separating and purifying polar analytes to the production of nutraceuticals, foodstuffs, and pharmaceuticals. However, additional experiments and clinical investigations are indispensable to gain a comprehensive understanding of its health benefits [5].

The distinctive core-shell structure and sporopollenin composition of pine pollen offer the potential for its application as a substance in delivery systems. The capability to load compounds is enhanced due to its substantial sacci volume and the porous sexine structure, which constitutes the outer layer of the pollen grain.

Moreover, pine pollen exhibits suitability for encapsulation owing to sporopollenin which is a component of its cell wall. Therefore, pine pollen holds promise as a carrier material across diverse applications [5].

In summary, this thesis explores the employment of pine pollen as the agent for producing PVP nanofibers. With its multifaceted biological properties and composition, pine pollen offers a range of potential applications, necessitating further experiments and clinical research for a more comprehensive understanding of its health benefits. As mentioned previously its unique features give it a capacity for compound loading make it an intriguing substance for incorporation in diverse delivery systems [5].

Zhou et al., worked on a study and proved that PP extract might improve the formation of collagen, the regeneration of granulation tissue and hair follicles, angiogenesis, and control the inflammatory process, which enhance the wound healing process. The study mentioned that its findings point to a high antioxidant and anti-inflammatory activity which benefits regenerative medicine [18].


Figure 3.1. Pine pollen dust.

### 3.3. COMBINING PVP AND PP FOR NANOFIBERS PRODUCTION

The investigation conducted in this scientific thesis explores the use of polyvinylpyrrolidone (PVP) in conjunction with pine pollen (PP) for the production of nanofibers, with the expectation of yielding distinctive outcomes. The inclusion of

pine pollen is anticipated to enhance the properties of the resulting nanofibers through the contribution of its diverse bioactive compounds and proteins. These natural constituents are envisioned to influence the biological, chemical, and mechanical features of the nano webs, consequently leading to the development of more stable, bioactive, and flexible fibers.

A study mentioned that through successful loading in the air sacs of pine pollen, researchers developed tablets that exhibited controlled release properties when combined with xanthan gum as a binder or coating of calcium alginate. These findings offer a potential solution for targeted intestinal delivery in medical applications, highlighting the versatility and effectiveness of utilizing pine pollen in pharmaceutical formulations [5].

The presence of natural and biocompatible compounds in pine pollen offers the potential to fabricate fibers possessing enhanced biocompatibility, thereby minimizing adverse reactions upon contact with biological systems. Importantly, the encapsulation and controlled release properties exhibited by PP make it a valuable component in the realm of drug delivery systems. Combining the remarkable characteristics of PVP (notably solubility) and PP (encompassing bioactive components) holds the potential to create nanofibers with enhanced properties.

An additional effect might be noticed from the incorporation of pine pollen is the potential enhancement of the electrocyclability of PVP, leading to the formation of well-aligned and uniformly distributed webs. In essence, the integration of pine pollen with PVP in the production of nanofibers using an electroblowing technique inspires synergistic effects that enhance the material features of the resultant fibers. To validate these hypotheses, a series of experimental studies were undertaken, and the outcomes were meticulously assessed and evaluated.

### 3.4. OTHER SUBSTANCES CAN BE USED WITH PVP FOR FAST DISSOLVING TABLETS

Several substances that can be considered to be used in the production of fast dissolving tablets. Some potential substances include:

1. Hydroxypropyl cellulose (HPC): HPC emerges as a promising option for enhancing antibacterial techniques in biomedical and pharmaceutical applications. Renowned for its remarkable water solubility, HPC is a cellulose material widely utilized in the field of biomedicine. Its notable attributes, including substantial biocompatibility, biodegradability, and antimicrobial activities, further contribute to its popularity in this domain [19].

2. Polyvinyl alcohol (PVA): PVA is a water-soluble synthetic polymer that can be used in fast dissolving tablets. It was mentioned in a scientific paper that in which they created a quick-dissolving method for delivering medicine by using honey and acetylsalicylic acid in nanofibers made from poly (vinyl alcohol) (PVA). These nanofibers are made using a natural deep eutectic solvent (DES)t, it was mentioned the nanofiber film made of PVA and DES can enhance the ability of enclosed drugs to dissolve quickly, making it suitable for fast-dissolving drug delivery [20].

3. Sugar-based bulking materials (e.g., mannitol and lactose derivatives): these can improve water solubility and sensory perception in fast-dissolving formulations, which means that these materials can be used in fast dissolving tablets applications [21].

4. Crospovidone: Crospovidone, also known as cross-linked PVP, is a polymer that acts as a superdisintegrant, helping the film absorb water faster without forming a gel [22].

5. Lubricants: Using lubricants in tablets makes them taste better when they break down in the mouth. It also makes the journey of the drug from the mouth to the stomach smoother because the tablets feel less gritty [21].

### 3.5. RELATED STUDIES THAT HAVE BEEN CONDUCTED PREVIOUSLY

Varma et al., developed capsules that were formulated from Meloxicam loaded into PVP: hydroxypropyl-β-cyclodextrin nanofibers, these capsules showed dissolution rate 7 times faster than free drug [14]. Maggi et al., prepared PVP30 electrospun fibers augmented with surfactants loaded with Firocoxib and they concluded that the electrospun fibers led to faster with more comprehensive dissolution of Firocoxib compared to the commercial reference product [14]. Shibata et al. recently found that the nanofibers made of polyvinyl alcohol (PVA) using the oil-in-water (o/w) emulsion electrospinning method could help dissolve poorly water-soluble drugs better [13]. Monteiro et al., used polycaprolactone nanofibers loaded with inclusion complexes of βCD and tetracycline HCL, which allowed a controlled release of the drug, with better antibacterial property [23].

# PART 4

# EXPERIMENTAL DESIGN AND METHODOLOGY

The main materials we aimed to use were PVP, PP, pure water, ethanol. Profiting from different scientific articles many ranges of concentrations were used to create to polymeric solution in order to obtain the best solution possible for a proper nanofiber with properties that can be convenient for the idea of application.

## 4.1. EXPERIMENTAL PROCEDURES

### 4.1.1. Fabrication of PVP-PP Nanofiber

The first step was to produce pure PVP nanofibers with no involvement of PP. The first experiment was done by using pure water and ethanol as a solvent. The solvent was made of 60% (w/v) ethanol, and 40% (w/v) water. A 50 ml polymeric solution was made, 12% (w/v) of the polymeric solution was PVP that dissolved in the solvent. This polymeric solution was approximately stirred for 4 h and then used in the creation of nanofibers by the electro-blown spinning method. The prepared solution was loaded into a syringe (needle), this needle was connected to a syringe pump.

Table 4.1. Parameters used in EBS.

| **Air pressure** | **voltage** | **Feeding rate** | **Collector-nozzle distance** |
|---|---|---|---|
| 1.5 bar constant air pressure | 20 KV | 15 mL/h | 35 cm |

Unfortunately, the produced nanofibers were full of droplets to the point that we can say the first experiment failed.


Figure 4.1. EBS machine.

Later on, a new polymeric solution was made but with using the same amount of both ethanol and pure water (solvent was 50% (w/v) pure water, and 50% (w/v) ethanol), in this solution we increased the PVP amount so that the polymeric solution contained 15% (w/v) of PVP. The polymeric solution was approximately stirred for 4 h and then used in the creation of nanofibers by the electro-blown spinning method. The prepared solution was loaded into the syringe (needle), the used parameters were the same as the first experiment (showed in Table 4.1). The produced nanofibers were also full of droplets and the experiment failed. Another experiment was made same solvent but the percentage of PVP was elevated to 20% (w/v). The solution was approximately stirred for 4 h. Parameters from Table 4.1 were used. The produced nanofibers also were full of droplets. Later on, another 100 ml polymeric solution was made using; 9% (w/v) PVP, 4.5% (w/v) carboxymethyl cellulose (CMC), 64% (w/v) water, and 22.5% (w/v) ethanol. Using the same fabrication method and the same parameters we obtained nanofibers but also high number of droplets were observed.

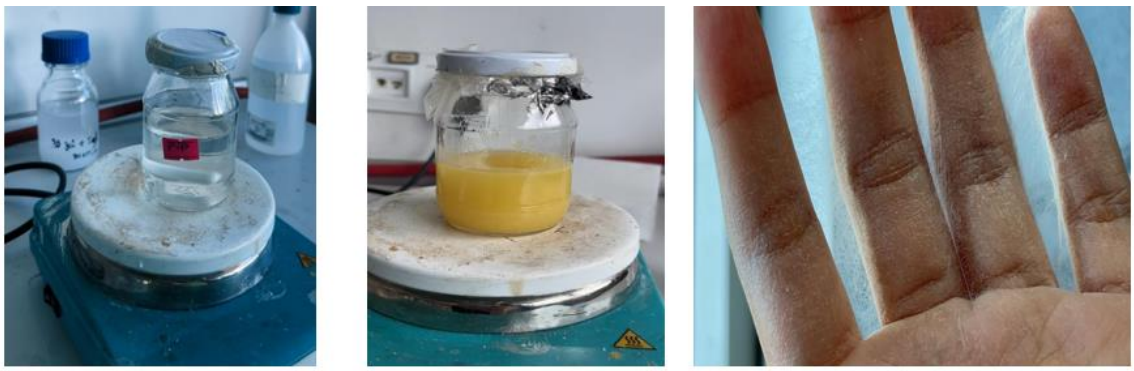
Subsequently, a new polymeric solution was made by only using ethanol as a solvent, the 100 ml polymeric solution consisted of (15% (w/v) PVP, and 85% (w/v) ethanol), the solution was stirred for 4 h, using the parameters from Table 4.1 we obtained nanofibers with better structure and no droplets were observed. After

obtaining PVP nanofibers successfully, a total of three other nanofibers samples that contain different amount of PP were needed to complete the experimental process. Concentrations used in the polymeric solutions are listed in Table 4.2 below.

Table 4.2. Concentrations used in the solutions.

| | **PVP** | **PP** | **Ethanol** |
|---|---|---|---|
| **Solution 1** | 15% (w/v) | - | 85% (w/v) |
| **Solution 2** | 14.85% (w/v) | 0.15% (w/v) | 85% (w/v) |
| **Solution 3** | 14.55%(w/v) | 0.45% (w/v) | 85% (w/v) |
| **Solution 4** | 14.25%(w/v) | 0.75% (w/v) | 85% (w/v) |

The three samples of nanofibers with different amounts of PP were successfully produced using EBS method with the parameters from Table 4.1. The three polymeric solutions were stirred for 4 h before the production process. It is important to mention that the substrate used to collect the nano mats was non-woven polypropylene.



(a) (b) (c)

Figure 4.2. (a) PVP-ethanol while being stirred, (b) PVP-PP solution, (c) pure PVP nanofibers.

Figure 4.3. Pure PVP nanofibers sample collected on non-woven polypropylene.

### 4.1.2. Crosslinking Treatment

Crosslinking methods are commonly used to enhance the properties of nanofiber such as improving the stability and mechanical properties. Conventional crosslinking methods, like chemical and enzymatic methods, can tend to toxic residues. Thermal crosslinking method which is known to be harmless with no toxic effects was used, it was executed in laboratory furnace. Selection of appropriate temperature and time is crucial in order to obtain enhanced and better characteristics. The produced mats underwent cross-linking at a temperature of 170 ℃ for a duration of 2 hours.


Figure 4.4. laboratory furnace.

## 4.2. CHARACTERIZATION TECHNIQUES USED TO EVALUATE THE NANOFIBERS

### 4.2.1. Fiber Morphology (SEM)

In order to examine the morphologies of the produced nanofibrous webs the Field Emission Scanning Electron Microscope FE-SEM brand name Carl Zeiss Ultra Plus was used. Measurements of one hundred diameter were taken for each sample from randomly chosen images. ImageJ software was used to manually check the average nanofiber diameters and their distribution.

### 4.2.2. Fourier Transform infrared Spectroscopy

Based on the interaction with infrared radiation the molecular composition of the produced samples were analyzed. Bruker ALPHA FTIR Spectrometer was used to obtain the Fourier Transformed Infrared (FTIR) spectra of the produced nanofibrous webs. an overall 24 scans were registered in the range of 400–4000 $cm^{-1}$.

### 4.2.3. Thermogravimetric Analysis (TGA)

In order to understand the thermal behavior of the produced fibers, Thermogravimetric analysis (TGA) was conducted. Samples were heated up to 500℃ in a nitrogen atmosphere at the heating rate of 10˚ C/min and a gas flow rate of 2 mL/min.

### 4.2.4. Mechanical Properties

A Shimadzu universal testing machine with a loading capacity of 1 kN was used in the examination of the mechanical properties like tensile strength (TS), maximum withstanding loads, and elongation of the produced samples. The tensile test was conducted with a tangential speed of 1 mm/min.

### 4.2.5. Water contact angle

To assess how water interacts with each sample's surface, and to obtain information about the hydrophobicity of the surface for the produced nanofibers, the contact angles of the samples was measured when a small droplet of pure water (about 0.0085 mL) was placed on them at room temperature. the measurement was performed using video contact angle measurement equipment called Theta Lite, and the samples were cut to 50 mm × 50 mm dimensions for this analysis.

### 4.2.6. Air Permeability

An air permeability tester called Prowhite Air test II was used in the examination of the air permeability of the produced samples at 25 °C and a circular area of 50 mm in diameter. In each test, 100 Pa of air was Implemented to the sample.

## 4.3. STORAGE AND BIOLOGICAL ACTIVITY TESTS

Biological activities of 5% pine pollen integrated nanofiber and pure pine pollen were tested during 90 days storage period. For this purpose, the samples were placed in polyethylene zip-lock bags and stored under ambient conditions in the dark. The samples were analyzed at the beginning of the storage period and on the 15th, 30th, 60th and 90th days. For the extraction process, 2 g of sample was mixed with 10 mL of ethanolic solvent (30% ethanol) and subjected to extraction for 2 h at 50 °C. After extraction, the samples were centrifuged at 6000 rpm for 10 minutes to separate the supernatant [24]. The collected supernatant was then stored at -18°C for total phenolic content, DDPH radical scavenging activity, ABTS radical scavenging activity and α-glucosidase inhibition activity analysis. The details of these analyses are presented as supplementary material.

### 4.3.1. Total phenolic content

The determination of Total Phenolic Content (TPC) included mixing 0.2 mL of the sample with 2 mL of Folin-Ciocalteu reagent and 1.6 mL of %7.5 Na2CO3 solution

in a test tube. After a 60-minute incubation period in the absence of light, the absorbance was measured at 765 nm using a spectrophotometer (Mecasis, Optizen POP, Daejeon, Korea). The obtained absorbance values were calibrated in reference to gallic acid equivalents (GAE) [25].

#### 4.3.2. DDPH radical scavenging activity

For DDPH radical scavenging activity, 0.1 g of the sample was blended with 3.9 mL of DPPH solution (25 mg/L) produced using methanol in a test tube. Following a 30-minute incubation period in darkness, absorbances at 515 nm were measured using a spectrophotometer (Mecasis, Optizen POP, Daejeon, Korea), in accordance with the method outlined by Brand-Williams et al. in 1995 [26]. The resultant results were measured and presented as trolox equivalents (mmol TE/g sample).

#### 4.3.3. α-glucosidase inhibition activity

In the α-glucosidase inhibition experiment, 50 µL of the extract was mixed with 1250 µL of 67 mM KH2PO4. Then, 50 µL of α-glucosidase was added to the test tube. The solution was thereafter placed in an incubator set at a temperature of 37°C for 5 min. Following that, 125 µL of a solution containing pNitrophenyl-β-D-glucopyranoside (10 mM) was added to initiate the reaction. After 20 minutes, the reaction was stopped by adding 2 mL of a solution containing Na2CO3 (100 mM). The measurement of the resultant mixture's absorbance was taken at a wavelength of 400 nm [27].

The α-amylase and α-glucosidase inhibitory activities were quantified as a percentage of inhibition using the formula below (Eq. 1):

$$\%\ \text{Enzyme Inhibition} = \frac{ABScontrol - ABSsample}{ABScontrol} \times 100 \qquad \text{(Eq. 1)}$$

Here, ABS control represents the absorbance of the control, and ABSsample denotes the absorbance of the samples. To make an appropriate comparison between pure

pine pollen and 5% pine pollen integrated nanofibers in the enzyme inhibition test, 20-fold dilution was applied to the pure pine pollen sample.

### 4.3.4. ABTS radical scavenging activity

Following the preparation of the ABTS test solution, including 7.5 mM ABTS and 2.45 mM potassium persulfate, the mixture was allowed to incubate in a light-protected environment at room temperature for 16 hours to stimulate the synthesis of the ABTS radical. The resultant stock solution was diluted with water to attain an absorbance measurement of 0.700 ± 0.02 at 734 nm. In parallel, the extracts were properly diluted using 0.2 M sodium phosphate buffer with a pH of 7.4. Subsequently, 50 µL of the diluted extract was mixed with 2000 µL of the ABTS radical solution, and the resultant combination underwent incubation in darkness for 6 minutes. Serial dilutions of trolox ranging from 0.1 to 2 mM were methodically made and treated to the same reaction with the ABTS radical. The absorbances of both the extracts and trolox solutions were later measured at 734 nm. The resultant results were measured and presented as trolox equivalents (mmol TE/g sample) [27].

# PART 5

# RESULTS AND DISCUSSIONS

## 5.1. MORPHOLOGICAL ANALYSIS OF ELECTRO BLOWN NANOFIBERS (SEM)

The examination by the scanning electron microscope was done and the morphological details of the samples are shown in the figure below.

Our results showed smooth with small amount of droplets rate. It is observed from figure 5.1. that the pure PVP nanofibers has comparatively thin nanofibers with an average diameter of around 1345.24 ± 4.53 nm. It is observed from figure 5.2. that the average diameter of PVP/1%PP is averaged around 1106.51 ± 54.53 nm which was lower in comparison with the pure PVP fibers. figure 5.3. it is depicted that PVP/3%PP nanofibers are exhibiting an average diameter of approximately 1081.83 ± 38.51 nm which is lower in comparison with the average diameter of both pure PVP and PVP/1%PP samples, it is illustrated from figure 5.4. that PVP/5%PP nanofibers are showcasing a mean diameter of approximately 1021.01 ± 20.86 nm which falls relatively close to the mean diameter of PVP/3%PP.

It is worthy to mention a previous study that mentioned the impact of PVP concentration in ethanol solution on nanofiber diameters, in the study nanofiber sizes increased from 120 nm at 2 wt. % PVP to 1500 nm at 10 wt. %, also the importance of the influence of solvent was mentioned [28]. which can explain the reduction in the average diameters as the percentage of PVP is decreasing. A different paper explained that the viscosity was increasing while PVP increased and stated that the average diameter was increasing as PVP concentration was increasing [29].

As a conclusion it was noted that the average diameters of the produced fibers decreased as the we reduced PVP concentration and the addition of PP to the solution that may modified the morphological properties of the PVP solution and caused changes in solution properties, such as viscosity or surface tension, which can affect the spinning behavior and thus result in different fiber diameters.

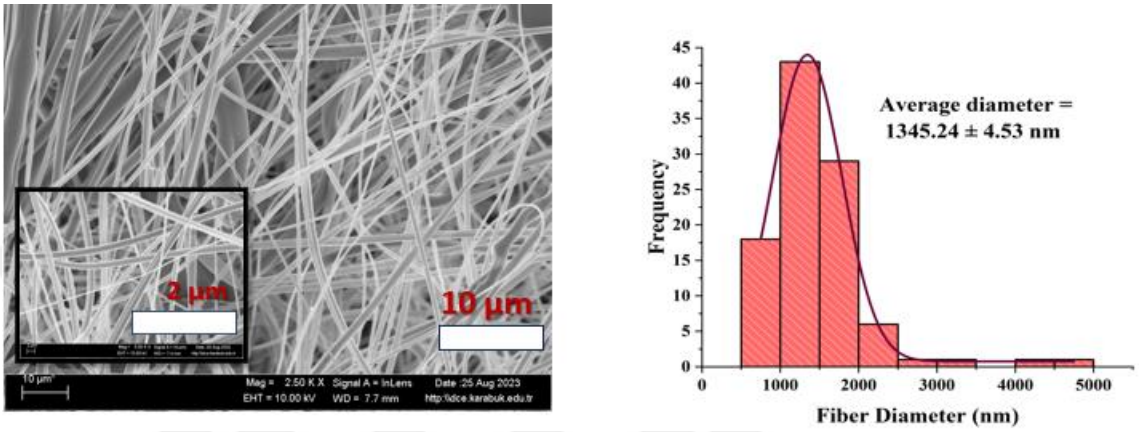



Figure 5.1. SEM images and fiber diameter distribution of pure PVP.

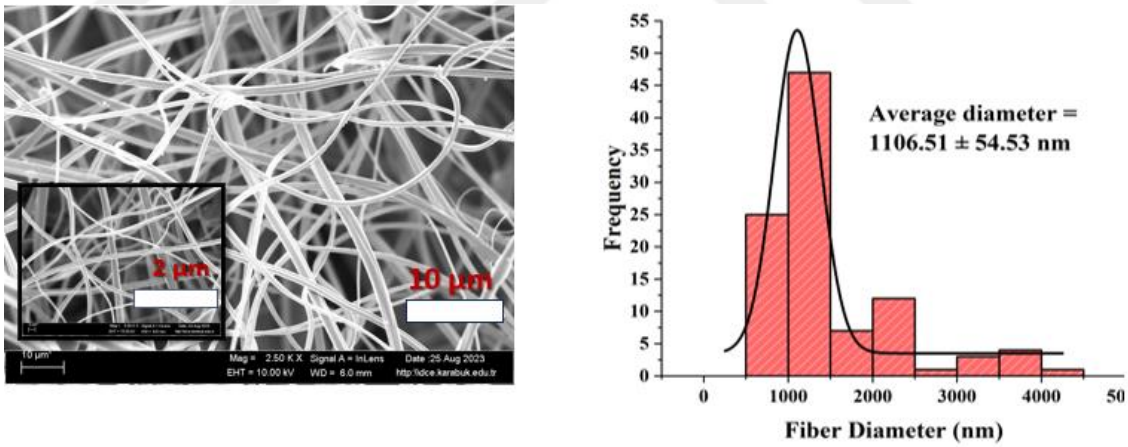



Figure 5.2. SEM images and fiber diameter distribution of PVP-1%PP.

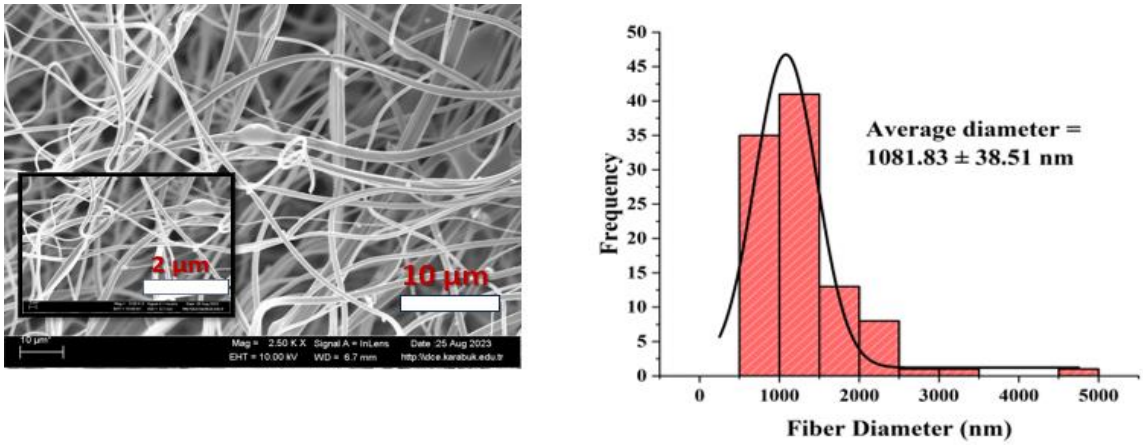



Figure 5.3. SEM images and fiber diameter distribution of PVP-3%PP.

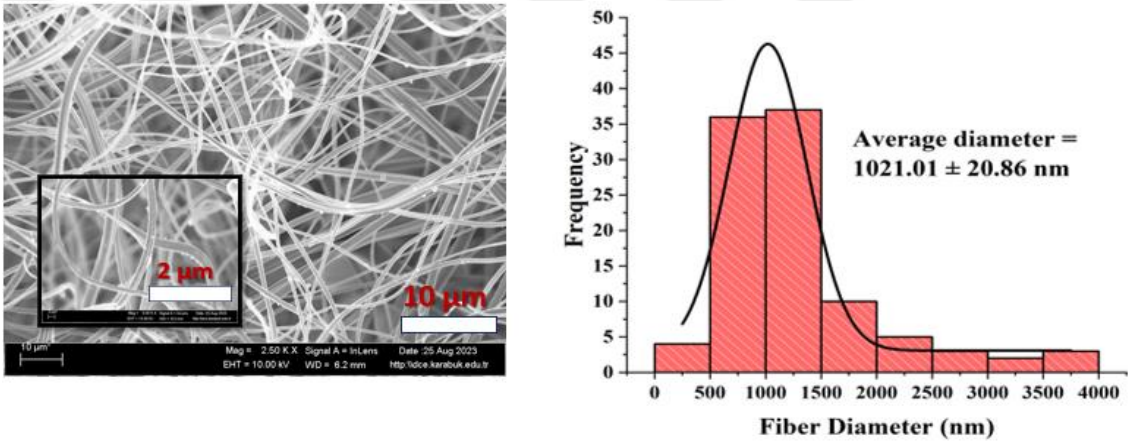



Figure 5.4. SEM images and fiber diameter distribution of PVP-5%PP.

## 5.2. FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

The FTIR spectra of pure polyvinylpyrrolidone (PVP) and the blended PP/PVP samples were illustrated as depicted in figure 5.5.

In the spectrum of the four samples infrared peaks were observed at 3418 $cm^{-1}$ which indicates O-H stretching [30]. The FTIR spectrum of the samples had a peak at 2950 $cm^{-1}$which indicates c-H stretching [30,31]. Thereafter, another peak was observed at 1655 $cm^{-1}$ wavenumbers which attributed to the stretching vibrations of C=O [32]. the peak at 1423.66 $cm^{-1}$ is assigned to the CH deformation of CH2 cyclic groups [30]. the peak observed at 1288 $cm^{-1}$ is attributed to C-N stretching [31].

In general, it was observed that adding PP to the PVP solutions showed no changes and no specific FTIR infrared peak in a comparison with the peaks of pure PVP webs, which means no new chemical bonds was formed. Thus, can be due the complete embedment of the PP in the fibers [30].

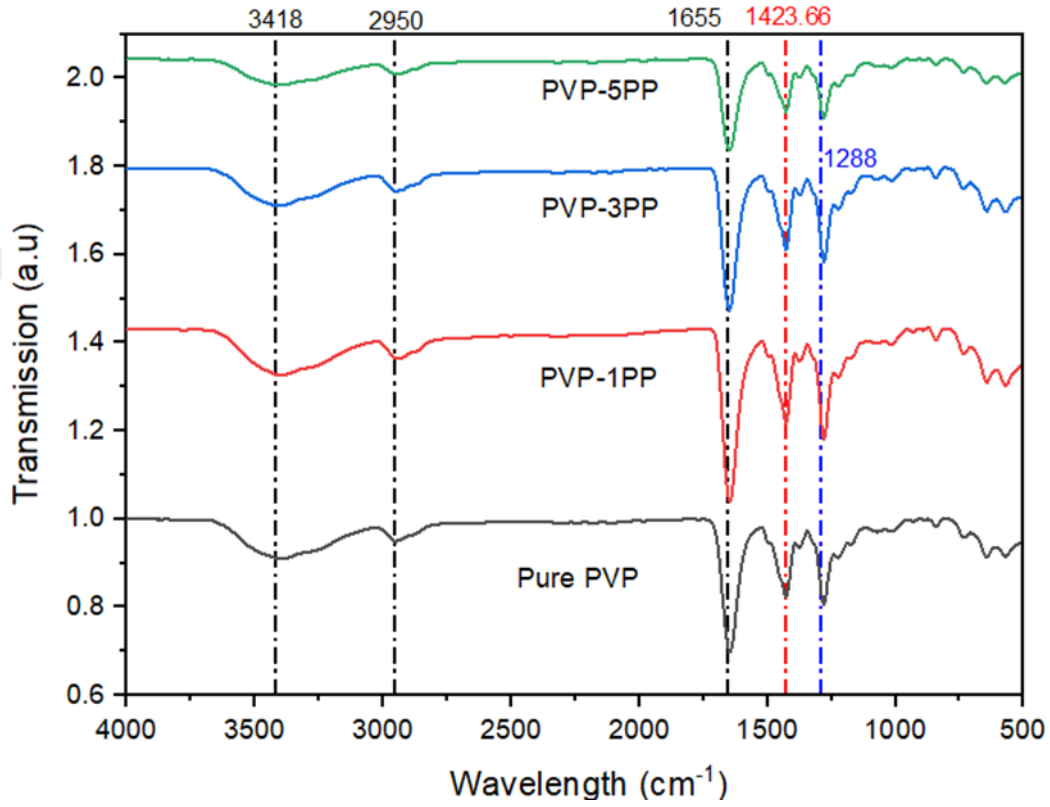



Figure 5.5. FTIR spectrum of PVP and PP/PVP nanofiber samples.

## 5.3. WATER CONTACT ANGLE

The surface wettability of the fiber webs was assessed by measuring the water contact angle. A higher angle indicates hydrophobicity or water repellency, while a lower angle suggests hydrophilicity or water absorption. It is commonly known that PVP exhibits hydrophilic properties and readily interacts with or dissolves in water. The fundamental occurrence is that the hydrophilic ingredients in the fibers increase the water solubility, on the other hand the hydrophobic ingredients decrease its solubility [30].

The recorded results of the contact angles were as follows: pure PVP had a contact angle of 27.72°, PVP/1PP had a contact angle of 38.33°, PVP/3PP had a contact angle of 39.64°, and PVP/5PP had a contact angle of 16.94°. All measured contact angles were less than 90°, indicating that the fiber webs possess wettability. Consequently, the produced webs can be considered hydrophilic due to the inherent hydrophilic nature of PVP [14].

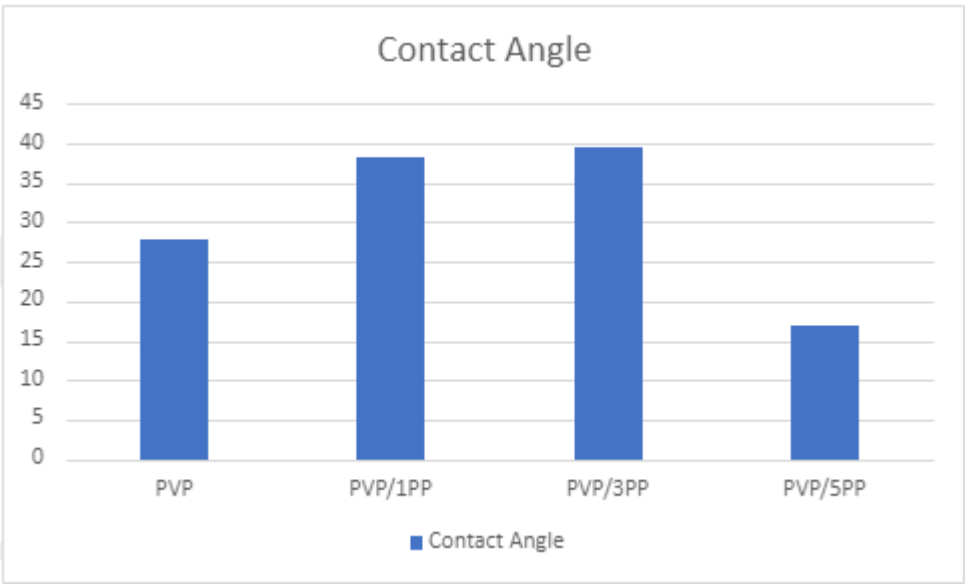



Figure 5.6. Contact angle values of the samples.

## 5.4. THERMOGRAVIMETRIC ANALYSIS (TGA)

To understand the thermal properties of the produced fibers, we analyzed its thermal behavior/ TG, DTA and DTG (thermogravimetric analyses) were performed within the temperature range of 25 to 500°C. The thermal degradation of the four samples is depicted in figure 5.7.

We can observe from the figure that the initial weight losses were approximately 11.82% for the four samples that may occurred because of loss of residual solvent, moisture and the water adsorption, which is similar to a prior study (Newsome et al., 2014) that was done on silica/Polyvinylpyrrolidone composite nanofibers, and it was reported that weight loss of the samples started before 100 °C because of the water adsorption [33].

Results showed that PP had an effect on the weight loss of PVP fibers. After the first 11.82% mass loss PVP-1PP and PVP-5PP which had a similar degradation behavior and a similar weight loss percentage showed nearly 72.496% weight loss between 385°C and 455°C. In the case of PVP-3PP, these fibers showed nearly 84.04 % mass loss between 210°C and 518°C. PVP also showed approximately 71.341% weight loss between 210°C and 518°C which is lower compared to the pure PVP sample weight loss. There was no more weight loss 520°C.

It can be observed from the results that the thermal stability was improved for PVP-PP webs. This is similar to a study done by Sharma, D., et al. (2023) that noted the improved thermal stability of the PVP-PEO blend [34].

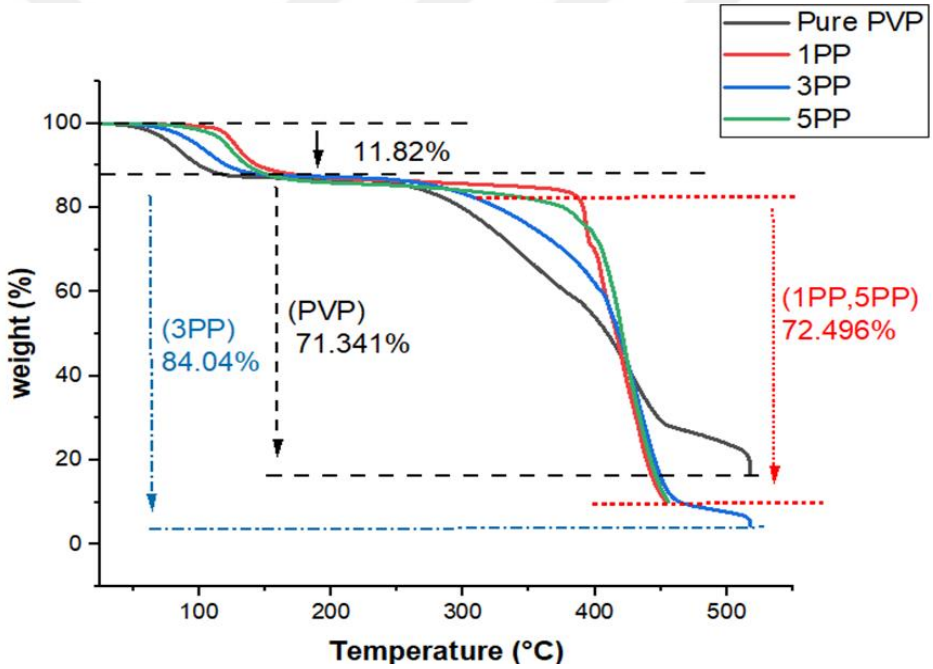



Figure 5.7. TGA results of the samples.

## 5.5. AIR PERMEABILITY

An air permeability test measures how easily air can pass through a material. It provides information about the material's porosity and allow the flow of air. Figure 5.8. displays the air permeability data. Depending on our findings it was observed that the air permeability of samples that contain 1% PP (65.2 mm/s) was lower than pure PVP (75.5 mm/s). Moreover, nanofibers containing 3% PP (49.8 mm/s) show

lower air permeability compared to both 1% PP and pure PVP. Similarly, the addition of 5% PP (48 mm/s) results in lower air permeability compared to nanofibers containing 1% PP, 3% PP, and pure PVP.

Pure PVP obtain the higher value, the incorporation of PP into PVP resulted in a decrease in air permeability. This can be explained by the idea that is mentioned in previous study explaining that fiber diameters, porosity, and thickness are parameters that can affect the air permeability of the fibers [35]. It was noted that the morphology of the obtained webs has a considerable effect on air permeability, nanofiber sizes have a major effect on the pore sizes which can influence the air permeability, pores with high diameters lead up to high air penetration [36].

All PVP/PP samples obtain average diameter that is less than the average diameter of pure PVP, which may be the reason of decreasing the air permeability as it was stated in a previous paper which explained that the air permeability was decreased with the reduction of diameter of the fiber [37].

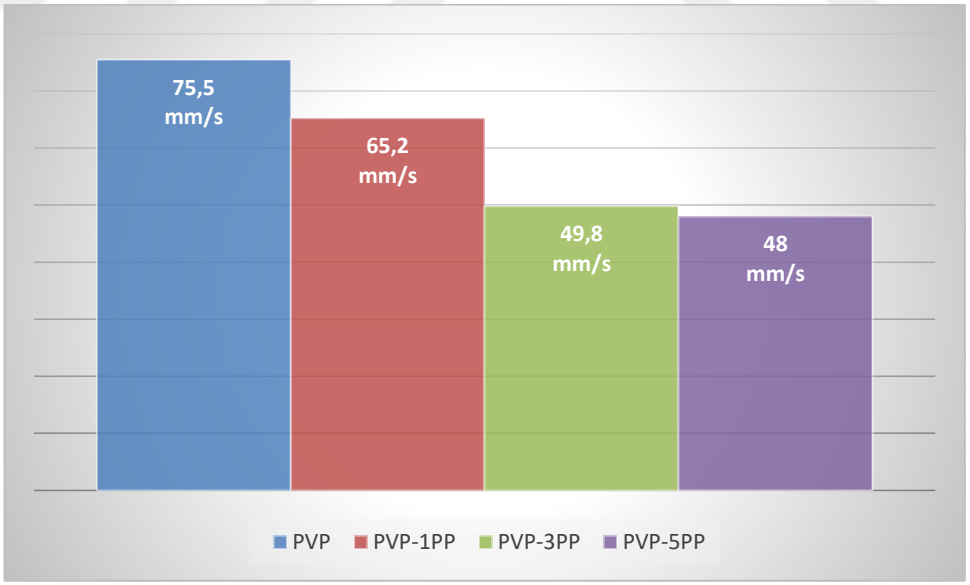



Figure 5.8. Air permeability test values.

## 5.6. MECHANICAL PERFORMANCE

To ensure the long-term sustainability the mechanical properties of the produced nanofibers were examined. The tensile strength and the elongation at break of the fibers are listed in Table 5.1 below.

It is observed from the results adding pine pollen improved the flexibility of the fibers as the fibers with PP owned better flexibility. in our results PVP/3PP possess the highest tensile strength (0.38 Mpa) as well as hold preference in terms of flexibility (Elongation at break= 8.11 %), all the other results are shown in Table 5.1.

When we stretch the fibers to test their strength, it's not just about what happens inside each fiber, the way they stretch and break is also affected by how they interact with each other. Chemical bonds between fibers, formed through crosslinking, act like bridges, making the overall structure stiffer. This stiffness means that when one fiber stretches, it pulls on its neighbors, influencing their behavior. So, the interactions between fibers, thanks to these chemical bonds, play a crucial role in determining the strength and behavior of nanofibers during testing [38].

In the context of a study described the presence of more agglomerates has a negative impact on mechanical stiffness. Therefore, in this specific case, more agglomerates are not considered better for mechanical properties which can explain the changes in the mechanical properties [39].

Table 5.1. Mechanical test results.

| Nanofibers | Tensile strength (Mpa) | Elongation at break (%) |
|---|---|---|
| PVP | 0.2 | 7.04 |
| PVP/1PP | 0.25 | 7.97 |
| PVP/3PP | 0.38 | 8.11 |
| PVP/5PP | 0.19 | 6.22 |

## 5.7.ANTIOXIDANT PERFORMANCE

Antioxidants are considered to be protective shields for our cells. They prevent the damages that are caused by the molecules called free radicals that have the ability to damage our cells [40]. Free radicals can cause various health problems like heart disease, inflammation, strokes, diabetes, rheumatic disease, liver issues, kidney problems, cancer, and even aging [41].

We conducted different antioxidant tests to evaluate the properties of our samples; the DPPH test, and the ABTS test.

For DPPH Antioxidant Activity PP shows a gradual decrease in DPPH antioxidant activity over time, starting at 2.95 μM TE/g and reaching 1.92 μM TE/g at 90 days, while PVP-5pp maintains relatively stable DPPH activity, with values ranging from 2.74 to 2.59 μM TE/g over the same period. The addition of PVP and the fibrous structure may contribute to this enhancement, which is similar to what was mentioned in a previous studies stated that Garcinia mangostana Extract GME/PVP fibers exhibit increasing in the antioxidant activity over pure GME [42].

On the other hand, the ABTS Antioxidant Activity results show that PP exhibits a significant decrease in ABTS antioxidant activity, declining from 8.61 μM TE/g at 0 days to 4.63 μM TE/g at 90 days. PVP-5pp also decreases in ABTS activity but retains higher levels compared to PP, ranging from 8.59 to 6.21 μM TE/g.

As a conclusion of these results, Both PP and PVP-5pp demonstrate antioxidant properties. PVP-5pp appears to maintain better antioxidant stability over time compared to PP.

It was concluded in a previous paper that after testing its effects in different ways, it was found that pine pollen extract has powerful antioxidant abilities and also can reduce inflammation. This suggests that it could be valuable in creating new herbal medicines for conditions related to oxidative stress and might be helpful for treating inflammatory diseases [41].

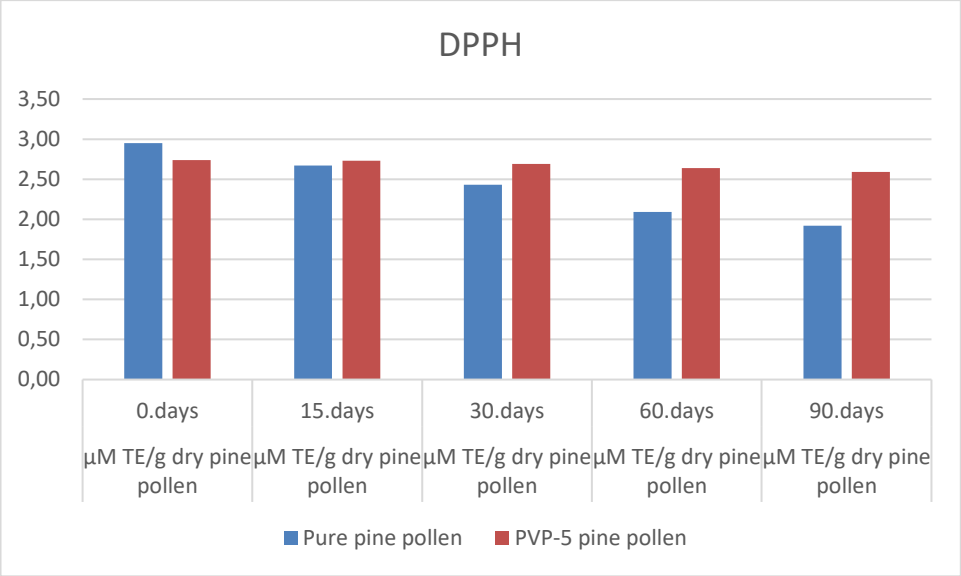



Figure 5.9. DPPH test values.

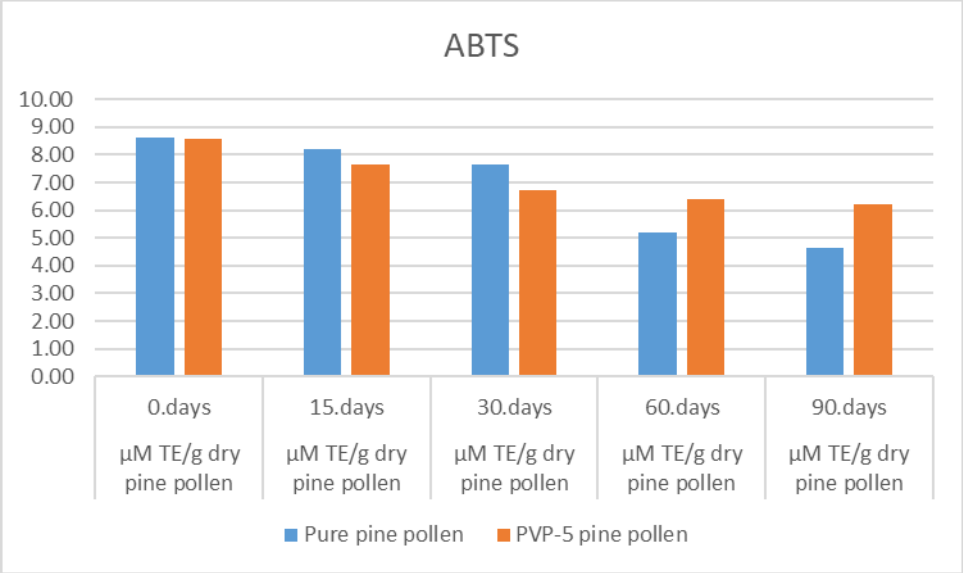



Figure 5.10. ABTS test values.

## 5.8.TOTAL PHENOLIC CONTENT

Pine pollen is an excellent source of phenolic compounds, including taxifolin, naringenin, p-coumaric acid, and epicatechin [43].

In our examination of total phenolic content during a 90-day storage period, we performed a detailed analysis of pure pine pollen and a novel formulation including 5% pine pollen incorporated into nanofibers.

The findings highlighted a specific temporal pattern within pure pine pollen, displaying a slow drop in total phenolic content during the storage period, underlining the inherent sensitivity of these chemicals to degradation. Specifically, the phenolic content for pure pine pollen fell from 2.82 mg GAE/g dry pine pollen at day 0 to 1.53 mg GAE/g dry pine pollen at day 90.

Contrastingly, the combined nanofiber samples revealed a considerable resistance against this degradation, consistently demonstrating greater total phenolic content compared to their pure pollen counterparts. Notably, the TPC of the nanofiber-integrated pine pollen sample displayed maintained stability within the integrated samples, with phenolic content values of 2.73 mg GAE/g dry pine pollen at day 0 and 1.92 mg GAE/g dry pine pollen at day 90. The encapsulation of pine pollen inside a PVP polymer to produce nanofibers in our work presents a possible protective mechanism against the degradation of phenolic compounds during storage. Nanofiber encapsulation may operate as a physical barrier, sheltering the encapsulated pine pollen from external elements such as oxygen, light, and moisture, known contributors to the destruction of bioactive chemicals. This encapsulation may have prevented the interaction between phenolic compounds and ambient factors, successfully reducing their exposure and susceptibility to destruction. The protective effect of nanofiber encapsulation accords with current research on the advantages of encapsulation methods, where the encapsulating material generates a microenvironment favorable to the stability of bioactive components.

In the context of our work, the integrated nanofiber samples underline the promise of this encapsulation method in retaining the overall phenolic integrity of pine pollen throughout storage.

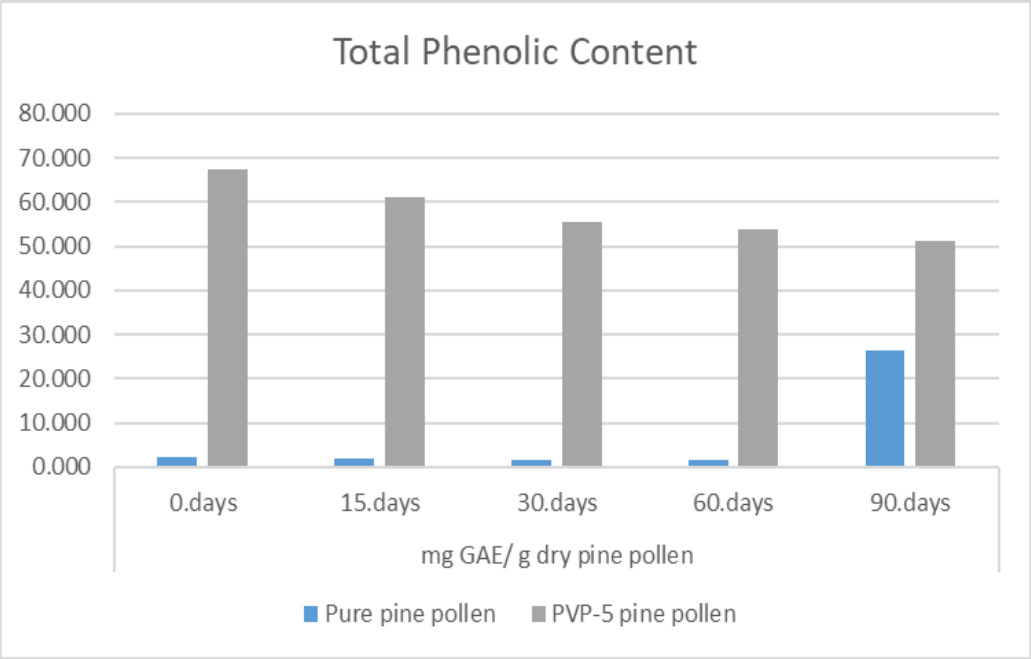



Figure 5.11. TPC test values.

### 5.9. α-GLUCOSIDASE ACTEVITY (%)

Within the scope of our study, α-glucosidase inhibition tests were conducted to assess the potential impact of pine pollen and its integration into nanofibers on this crucial enzyme. α-glucosidase is an important enzyme that works on breaking down carbohydrates and assist its intestinal absorption. suppression the action of this enzyme has the potential to lower blood glucose levels after meals, particularly in individuals diagnosed with type 2 diabetes [33].

the α-glucosidase activity in pure pine pollen (PP) exhibited a notable decrease over the 90-day storage period, declining from an initial activity of 62.51% to 26.44%. This decline indicates a progressive reduction in enzyme activity over time. In comparison, the formulation containing 5% pine pollen integrated into PVP polymer nanofibers (PVP-5pp) demonstrated a more stable α-glucosidase activity. Commencing at 67.23%, it decreased to 51.26% over the same storage period, showcasing a more effective retention of enzyme activity compared to pure pine pollen.

The observed α-glucosidase inhibition in both pure pine pollen and PVP-5pp suggests that pine pollen, whether in its pure form or integrated into nanofibers, holds potential as a beneficial strategy for controlling blood sugar levels.

The observed decrease in α-glucosidase inhibitory activity, as evidenced by the decline in enzyme activity over the 90-day storage period, aligns with the diminishing levels of phenolic substances in both pure pine pollen (PP) and the formulation integrating 5% pine pollen into PVP polymer nanofibers (PVP-5pp), as discussed earlier. Phenolic chemicals are known to display bioactive features, including anti-diabetic benefits, by interfering with the action of enzymes involved in glucose metabolism. The large fall in phenolic content in both PP and PVP-5pp may contribute to the observed decline in α-glucosidase inhibitory action.

As phenolic compounds exhibit antioxidant qualities, their breakdown over time, especially in the case of pure pine pollen, might make them less efficient in blocking α-glucosidase. Moreover, the protective effect of nanofiber encapsulation in PVP-5pp may have buffered the degradation of phenolic compounds to a certain degree, explaining the considerably more stable α-glucosidase inhibitory efficacy compared to PP. This correlation between phenolic content and enzyme inhibitory activity underscores the potential role of phenolic substances in influencing the anti-diabetic properties of pine pollen and suggests that the protective effect of nanofiber encapsulation could contribute to the preservation of these bioactive compounds.

This finding is consistent with previous research emphasizing the examination of pine pollen in clinical studies for its potential in managing various health issues, including type 2 diabetes mellitus, either as a standalone treatment or in combination with other therapeutic approaches [39].

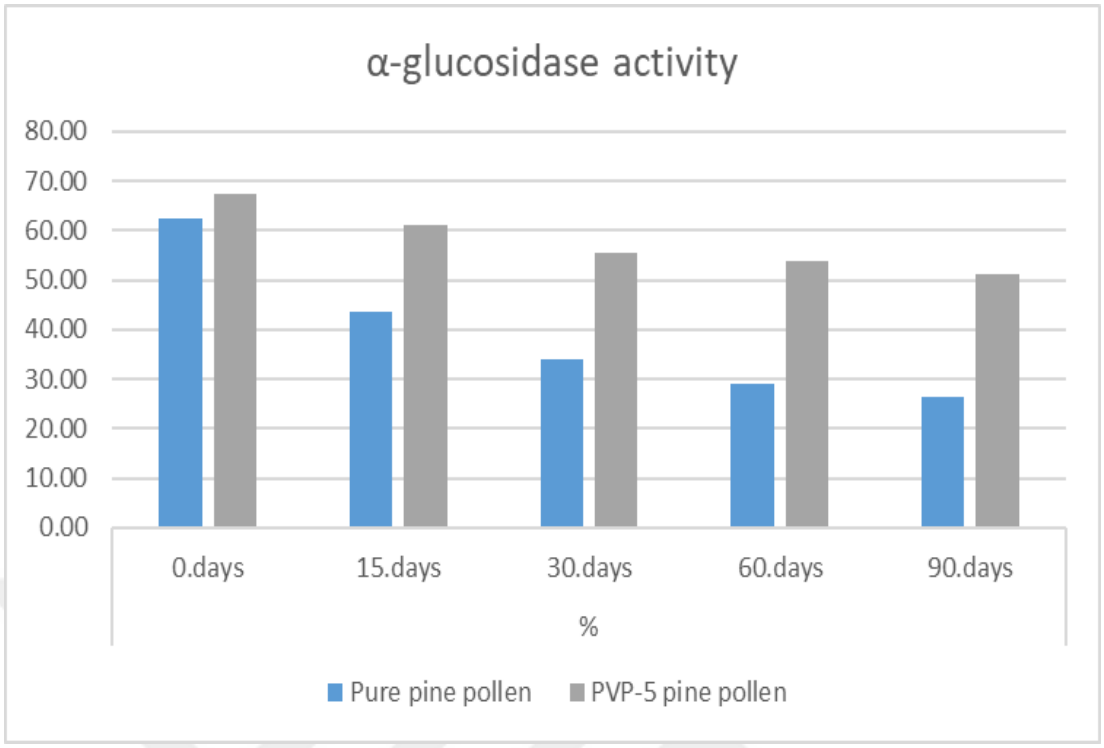



Figure 5.11. α-glucosidase test values

## PART 6

## CONCLUSION

As a conclusion, the electroblowing process was successfully used to fabricate nanofibers from pure Polyvinylpyrrolidone (PVP) and PVP/ pine pollen (PP) blend for fast dissolving tablets applications. The electroblown nanofibers demonstrated unique characteristics and functionalities. The incorporation of pine pollen into the PVP nanofibers was confirmed through careful characterization, all fibers exhibit hydrophilicity, and the produced fibers exhibited remarkable antioxidant properties. Our tests indicated that the antioxidant properties inherent in pine pollen were effectively preserved in the PVP nanofibrous matrix. This preservation of antioxidant activity is of significant importance as it broadens the potential applications of PVP nanofibers, offering not only structural benefits but also functional attributes. Furthermore, considering the α-glucosidase activity test results these nanofibers hold potential for applications related diabetes. In light of these findings, pine pollen-incorporated PVP nanofibers emerge as a promising candidate for fast dissolving tablets, particularly in the context of diabetes treatment or prevention. The synergistic combination of structural integrity and antioxidant properties in these nanofibers could pave the way for innovative solutions in the development of therapeutic materials for managing oxidative associated disorders and diabetes in the form of fast dissolving medication.

To further assess the release kinetics of active components from nanofiber-based tablets, in vitro dissolving some studies can be recommended to the extensive characterization testing conducted in our work. This will offer important details about the drug's release profile and dissolving behavior, which are crucial for optimizing the formulation for clinical efficacy. Furthermore, cytotoxicity analyses can be carried out to assess the biocompatibility of the tablets that have been

manufactured and guarantee their safety for possible medical uses. Furthermore, stability studies conducted under

various storage settings would be helpful in assessing the long-term stability and shelf life of formulated tablets, which are critical for marketing and real-world applications. All things considered, by carrying out these further experiments, we can learn more about the functionality, stability, and safety of PVP nanofiber tablets containing pine pollen, opening the door for their eventual development into successful diabetes management treatments.

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## RESUME

Jvana ABI completing her primary and most of the secondary education in the same city. She graduated from high school in Gaziantep. In 2017, she began her education at Karabuk University, Faculty of Engineering, Biomedical Engineering Department, graduating in 2021. In 2022, she initiated her master's program at Karabuk University, Institute of Graduate Programs, Department of Biomedical Engineering.