International Journal of Electrical Engineering & Emerging Technology, Vol. 04, No. 02, DEC 2021, pp 51-56

# "Ultrasound Mediated Smart Drug Delivery System, a Noninvasive approach for the delivery of Insulin from Nanofiber Film

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[**Received on:** 17/11/2021 **Accepted on**: 26/11/2021 **Published on:** 04/12/2021]

***Abstract* — Diabetes mellitus is a metabolic disease defined by high blood glucose levels that cause long-term damage, dysfunction, and failure of many organs, particularly the eyes, kidneys, nerves, heart, and blood vessels. Diabetic individuals with severe diabetes mellitus require insulin injections, which is an intrusive and painful approach to provide the medicine. Researchers hope to improve a diabetic patient's quality of life by developing a noninvasive insulin administration system. The goal of this study was to create a smart medication delivery device that released inulin (HUMULIN 70/30) in a burst and sustained manner. The biodegradable polymer PVA was employed to generate drug-loaded transdermal nanofiber films using the electrospinning process in this system. PVA and Zein FTIR spectra are completely soluble with the medicine (HUMULIN), and Peaks revealed that the drug does not react with polymers. The PVA Nanofiber sheet was expanded by 200 nm after encapsulating the medication, according to SEM data. In PVA, the release of the HUMULIN 70/30 drug obeyed the Higuchi drug release model value of the coefficient of correlation (r2= 0.9411). The drug release from the PVA follows the Super Case II transport mechanism, according to Korsmeyer's model. In terms of drug release in PVA, the Ninhydrin test yielded positive results (violet hue). The drug was successfully delivered into the recipient sheet using ultrasound waves.**

## I. INTRODUCTION

Diabetes mellitus is an upset, consistent with WHO, approximately 422 million people are affected by diabetes everywhere the globe [1]. In Pakistan, the primary survey [National Diabetes Survey of Pakistan (NDSP) 1994–98] revealed 8.7% prevalence [2]. Since that time, small-scale studies including a survey of Pakistan Health Research Council (PHRC) reported prevalence between 13.1 and 26.9%. A most up-to-date study [2nd NDSP 2016–17] evaluated that around 26.3% of the local population above 19 years of age, is diabetic [Known diabetics; 19.2%, newly diagnosed diabetics; 7.1%]. the resut shows an increased ratio compared to the first NDSP (Urban; 22.04% and rural; 17.15%) [3-4]. Diabetes is caused by the imbalance of an anabolic hormone present within the body called "insulin". Insulin is accountable for permitting glucose within the blood to enter cells, providing them with the energy to function. The motivation of this research paper is to boost delivery methods of insulin which will overcome the barriers to insulin absorption.

**IINSULIN ADMINISTRATION BY ORAL ROUTE:** Among the assorted insulin administration methods, the oral route is that the most convenient. Oral insulin development remains within the works. Proteins like insulin have a bioavailability of but 1% when taken orally. As a result, a goal has been set to reinforce it to around 30%–50%. Insulin is destroyed by the acidic environment of the stomach, which is mediated by enzymes like pepsin, trypsin, and peptidase. Insulin degrading enzymes (IDEs), also called cytosolic enzymes, are enzymes that break down insulin before it reaches its target. [5]. **INSULIN ADMINISTRATION BY BUCCAL ROUTE:** Insulin is delivered through the buccal mucosa within the kind of spraying. Because the buccal mucosa includes a low permeability, additional puffs are necessary. By adding some insulin absorption enhancers, we will boost its permeability. However, if we add insulin absorption enhancers, we will still deliver 12 percent of the insulin to the target. [6] **INSULIN ADMINISTRATION BY INHALED ROUTE:** Insulin is delivered through the lungs during this method. Because of the dearth of specific digestive enzymes, it's a bigger extent and doesn't contain any barriers just like the other two routes. However, more insulin is required to achieve the aim. And also the rate of insulin absorption varies with age. Inulin's bioavailability ranges from 9% to 22%. [7]. **INSULIN ADMINISTRATION BY TRANSDERMAL ROUTE:** the foremost promising method of insulin delivery through the in within the type of a patch is that the transdermal route. There are numerous advantages to using this route, but because of the massive molecule of protein, it's difficult to deliver the drugs to the organ [8]. The applying of an external source of ultrasound to the skin increases its permeability by 80% to 90%. This system typically employs a low-frequency range of 1 to three.5 MHz. Some case studies suggest that ultrasound improves skin

delivery.[9].

1- Chien et al. created a noninvasive drug delivery technique for controlled peptide delivery to various organs and tissues. They discovered that using ultrasound to facilitate transdermal transport of peptides [10].

2- Guo et al. prepared insulin-containing lecithin vesicles and estimated the effect of ultrasound on a transdermal drug delivery system. They concluded that these vesicles could be a good carrier for insulin delivery the via transdermal route when combined with ultrasound [11].

3- Park et al. investigated the utility of a lightweight cymbal transducer array for transdermal insulin delivery. They concluded that the cymbal array was a useful system for transdermal insulin delivery [12].

4- Martanto et al. created solid microneedles for transdermal insulin administration to lower plasma glucose levels. They concluded that arrays of microneedles using ultrasonic waves can improve permeability.14]

## II. Objective

1-The goal of this study is to create a transfer Nanofibrous patch that can deliver insulin into the bloodstream when exposed to ultrasound.

2- To further investigate the effectiveness of ultrasound in increasing skin permeability.

## III. Research Approach

Electrospun was used in this study. Nanofibers are being used as nanofibers as an insulin career shows promising results in treating the disease without any side effects. Nanofiber are a novel approach to insulin delivery that prevents insulin decomposition before it reaches the target. The process of electrospinning results in the formation of nanofibers. It is the most common and simplest method of producing nanofibers. Electrospun nanofibers are particles that range in size from 1–1000 nanometers in width, which is nearly a thousand times smaller than a normal cell in the human body [15]. Because of their small size, adaptability, and high surface-area-to-volume ratio, they are ideal for drug delivery. Metals, polysaccharides, and proteins can all be used to create eelectrospunnanofibers. Organic protein-based nanoparticles such as silk, keratin, collagen, elastin, corn zein, and soy protein-based nanoparticles are extremely useful in terms of biodegradability, bioavailability, and overall effectiveness. [16].

## IV. Materials And Methods

In this study, electrospun was used. Nanofibers as an insulin career show promising results in treating the disease with no side effects. Nanofibers are a novel method of insulin delivery that prevents insulin decomposition before it reaches the target. Nanofibers are formed as a result of the electrospinning process. It is the most common and straightforward method of creating nanofibers. Electrospun nanofibers are particles with a width of 1–1000 nanometers, which is nearly a thousand times smaller than a normal cell in the human body [15]. They are ideal for drug delivery due to their small size, adaptability, and high surface-area-to-volume ratio. Electrospun nanofibers can be made from metals, polysaccharides, and proteins. Silk, keratin, collagen, elastin, corn zein, and soy protein-based nanoparticles are extremely useful in terms of biodegradability, bioavailability, and biocompatibility.

### *A. Characterization Of Nanofibrous Sheet*

1- FTIR (Chemical Interaction Analysis)

Fourier Transform Infrared Spectroscopy (FTIR) is an analytical and diagnostic method for identifying organic, polymeric, and, in some cases, inorganic materials. Infrared light is used in this method to perform scanning itoperceive chemical properties. FTIR spectroscopy was used to examine the chemical structure of nanofibers. Origin Pro 8 software was used for data analysis and curve fitting.

**Results Of Pure PVA/Insulin Encapsulated PVA**

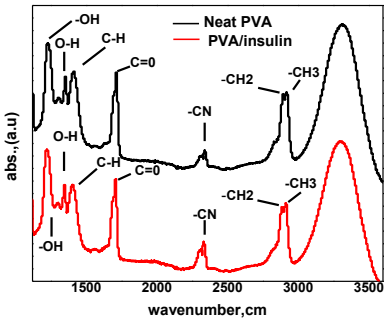


Figure 1(a) depicts the PVA spectrum bands at 1148 cm1 (OH stretching), 2925 cm1 (CH2 stretching), and 2960 cm1 (CH2 stretching) (CH3 stretching). The presence of water, which is absorbed by PVA molecular chains, is responsible for the very broad banbroadband480 cm1. The band at 1329 cm1 in the FTIR spectrum of pure PVA was caused by the coupling of the O–H in-plane vibrations, and the band at 1420 cm1 was caused by the C–H wagging vibrations [17].

2- SEM (Morphological Analysis)

The morphology of electrospun nanofibers was studied using scanning electron microscopy (SEM) [19;]. The SEM picture in the figure below depicts a) neat PVA and b) insulin encapsulated PVA. The diameter of tidy PVA nanofibers ranges from 99 nanometers to 230 nanometers, with 99 nm being the norm. PVA/Insulin nanofibers have diameters ranging from 99 to 330 nanometers. PVA with drug encapsulation has an average diameter of 120 nm. As a result, the average diameter of the PVA fibers continued to rise.

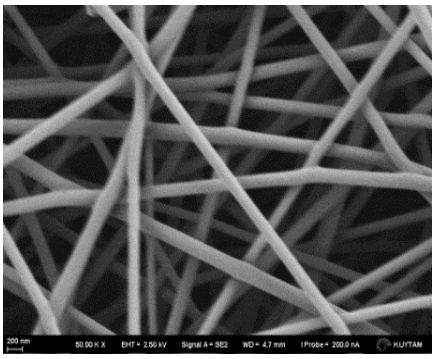

Figure (a1) neat PVA nanofibers

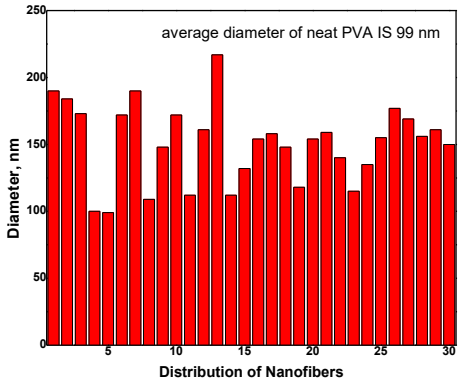


Figure (a2) neat PVA

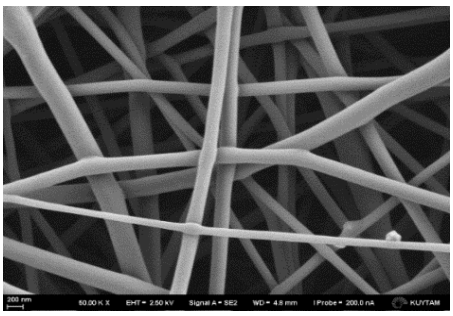

Figure (b1) Drug (insulin) encapsulate

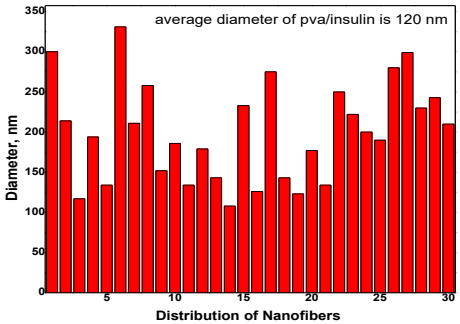


Figure (b2) Drug (insulin) encapsulated PVA

**MORPHOLOGY OF PVA FIBER**

### *B. Release Behaviour Of Drug From Nanofibrous Sheet Through Uv-Spectrophotometer*

The release behavior of insulin from insulin-loaded PVA nanofibers and insulin-loaded zein nanofibers in PBS solution was studied using the UV-1800-VIS Spectrophotometer at various concentrations: 10 ppm, 20 ppm, 30 ppm, 40 ppm, and 50 ppm. Insulin has a typical peak at 271 nm in optical wavelength. Using a digital scale, the insulin-loaded PVA NF film was carefully peeled off and accurately weighted. 20 mg of drug-loaded PVA NF film (containing around 0.5ml of insulin) was immersed in 10ml PBS and swirled by hand at 37°C. Samples were taken and replaced in solution after one minute, and UV–vis spectroscopy was performed; samples were replaced in solution to verify that new samples reflected cumulative release. Figure 3 shows the UV–vis spectra of release from PVA NF Film immersed in PBS solution (a). Electrospun PVA NF film insulin release profile. As far as the Higuchi model is concerned. The UV–vis spectra of release from PVA NF Film submerged in PBS solution are shown in Figure 3(a). Insulin release profile from electrospun PVA NF film. The Higuchi model, as shown in the following equation, is a widely used model for studying drug release behavior.

$$KHt1/2 = Mt / M\ 100$$

The mass of the drug supplied at time t is denoted by Mt.
M is the amount of medicine released per unit of time (t).
Higuchi's Dissolution Constant is denoted by kH.
t=time

We may interpret the drug release mechanism as a diffusion-based system since the correlation coefficient is higher. controlled release mechanism. After learning about the release mechanism called Diffusion Control from Higuchi's It's important to figure out what kind of dispersion this release behavior follows in order to create a model. To further understand this form of dispersal, the model was fitted to the release date.

Korsmeyer–Pappas' empirical equation is as follows
The mass of the drug supplied at time t is denoted by Mt.
As t =, M=the amount of medicine released.
k denotes a constant rate of release.

n=The drug release exponent, according to Korsmayer–Pappas. Using NF matrices, this equation calculates the mass of drug release with time. The release rate constant k is linked to delivery mechanism and pharmaceutical qualities, whereas n is the diffusion exponent that describes diverse release processes (table1). To analyze release kinetics, a graph is created between log cumulative percent drug release log(Mt/M) vs log time (log t). The value of n is used to categorize different types of release mechanisms. The features of the Kinetic Models utilized to explore the insulin release behavior of PVA NF film are summarized in Table 2. In-vitro.

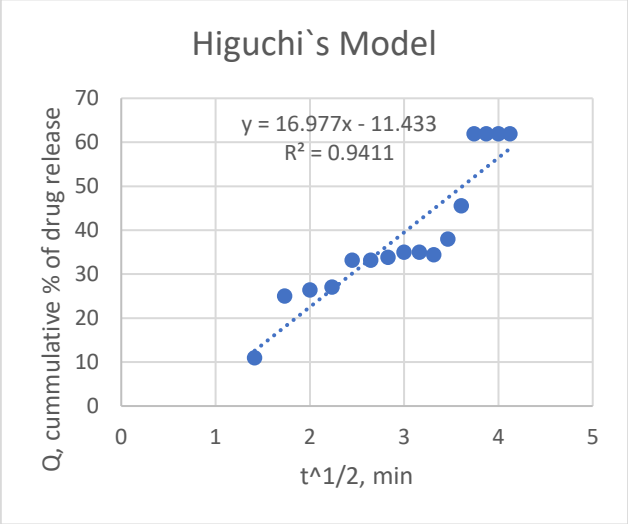


Figure 2(a) shows the PVA's R² value of Higuchi model.

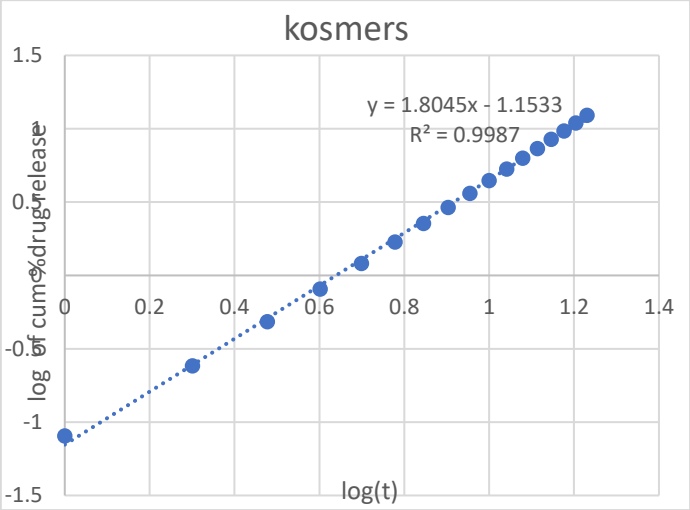


Figure 2(b) shows the PVA's R² value KORSMEYRS- Peppas model.

### *C. Making Of Skin Substitute For In Vitro Testing*

PCL (10wt%) was first dissolved in a chloroform/methanol (2:1, v/v) solvent mixture by stirring it at 500 rpm for 2 hours at room temperature using a magnetic stirrer. Gelatin (50 percent w/w) was dissolved in formic acid (80 percent v/v) by stirring at 500 rpm for 3 hours at room temperature [21]. Following the preparation of both polymeric solutions, the PCL and gelatin solutions were mixed 60:40 and agitated for 2 hours. The gelatin solution was dispersed in the PCL solution after 2 hours of stirring, resulting in an immiscible PCL/gelatin combination (emulsion) that was used for electrospinning. To produce skin replacement via electrospinning, the PCL/gelatin solution was placed into a 2 mL plastic syringe with a flat needle with a 0.56 mm tip diameter. With a feed flow rate of 0.1 mL/h, the applied voltage was adjusted to 22.5 kV

### *D. Behavior Of Ultrasonic Waves in Insulin Delivery*

Ultrasound is defined as sound with a frequency greater than 18 kHz. The piezoelectric effect underpins the majority of current ultrasonic equipment. This is accomplished by applying pressure on quartz crystals and some polycrystalline materials, such as lead-zirconated-titanium or barium titanate, which causes electric charges to form on the material's outer surface. Thus, applying a quickly alternating voltage across the opposing sides of a piezoelectric crystal causes matching alternating dimensional changes, turning electrical energy into vibrational (sound) energy [23]. The ultrasonic wave is a longitudinal wave (i.e. the direction of propagation is the same as the direction of oscillation). Longitudinal sound waves compress and expand the medium at a half-wavelength distance, causing pressure fluctuations in the medium. The resistance of the medium to sound wave propagation is determined by the acoustic impedance (Z), which is proportional to the mass density.[24 Based on frequency range and application, there are three main kinds of ultrasound conditions. 1-In clinical imaging, high-frequency or diagnostic ultrasound (3-10 MHz). 2-Ultrasound therapy with a medium frequency or therapeutic ultrasound in physical therapy (0.7-3.5 MHz). 3-Ultrasound with low or high frequency or power for lithotripsy, cataract emulsification, liposuction, cancer treatment, dental descaling, and ultrasonic scalpels (18-100 kHz). [25]

### Cavitational Effects Occurs in Low-Frequency Ultrasound

Cavitation is defined as the creation of gaseous cavities in a medium as a result of ultrasonic exposure. The fundamental source of cavitation is a pressure change in the medium caused by ultrasonic. Cavitation is the fast expansion or collapse of a bubble (inertial cavitation) or the slow oscillating motion of a bubble in an ultrasonic field (stable cavitation). When cavitation bubbles collapse, a shock wave is released that can induce structural changes in the surrounding tissue [26]. Tissues include air pockets trapped in fibrous structures, which behave as cavitation nuclei when exposed to ultrasound. The cavitation effects are inversely proportional to the frequency of the ultrasound and directly proportional to the intensity of the ultrasound. Cavitation may be crucial when using low-frequency ultrasound, exposing gassy fluids, or exposing tiny gas-filled areas. With the development of transdermal delivery as an essential method of systemic drug administration during the last two decades, researchers have been examining the potential application of ultrasound for transdermal delivery systems. The phenomena of ultrasound have been thoroughly shown utilizing numerous molecules at various frequencies ranging from 20 kHz to 16 MHz. In the early experiments, therapeutic ultrasound was the most widely employed frequency. The ultrasound settings were chosen initially to avoid potential safety difficulties, with frequencies ranging from 0.75 to 3.00 MHz and intensities ranging from 0.0 to 2.4 W/cm2. The biggest effect of low-frequency ultrasound (frequencies below 100 kHz) on transdermal transport has been discovered. Low-frequency ultrasound (48 kHz) was found to improve transdermal insulin delivery across diabetic rat skin [27].

**Effect of Ultrasound on Drug Encapsulated Sample.**

The most promising capacity for transdermal medication delivery is ultrasound. Because of vibrational energy, it has the potential to force the medication through the skin. An ultrasonic probe was utilized on a sample to assess the effectiveness of the United States. This sample is made up of three layers: a drug-containing nanofiber film, a skin layer in the center, and a receiver film on which the results were seen. A 3.5 kHz frequency was applied to the sample for half an hour. Following that, Ninhydrin testing was performed to determine the presence of protein in the sample, as insulin is a protein. **NINHYDRIN TESTING** is a qualitative test for amino acid analysis [28]. Insulin is a protein that contains 51 different kinds of amino acids. Amines react with Ninhydrin to produce a complicated blue-purple compound. We collected those samples and used ultrasonic waves on them for half an hour to test if the drug was transmitted from the drug-loaded film to the recipient film. All of the samples were split in half and put on a Petri plate. Following that, we apply two to three drops of Ninhydrin solution to each sample via a droplet. After 5 minutes of heat (100o C), the color of the sample turns purple, indicating that the recipient nanofiber film absorbs the drug from an external ultrasonic source. The project's goal was met with success.

## V. CONCLUSION

The obtained medicated Nanofiber sheets exhibit high compatibility with no chemical reactions. The FTIR spectra of PVA show that it is extremely miscible with the medication (HUMULIN 70/30). Peaks demonstrated that the medication did not react with polymers. The Nanofiber sheet has an average diameter of 120 nm and a diameter of 200 nm, according to SEM data. After encapsulating the medication, the overall size of the sheets grew. The medication HUMULIN is released from the system by the Higuchi drug release model's coefficient of correlation (r2= 0.9411) in PVA. The medication is released from the PVA via the Super Case II transport mechanism, according to Korsmeyer's model. In terms of drug release in PVA, Ninhydrin testing yields positive findings (violet color). The drug was effectively delivered into the recipient sheet using ultrasound waves.

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