

Advanced Transdermal Nanofiber Patch for Rapid Wound Repair

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ABSTRACT

Wounds due to diabetic foot ulcers affect 6.3% of the global population. It present a serious challenge in wound healing which often leads to chronic, non-healing wounds and, in severe cases also amputation. These complications arise when blood supply is adequent which also makes traditional treatments less effective. Therefore, the aim of this study was to develop a nanofibrous patch for controlled transdermal drug delivery to effectively heal diabetic wounds. Two most important materials where used for sustained drug delivery i.e. polycaprolactone (PCL) and Bixin. PCL which is a biodegradable polymer with a slow degradation rate was used as the base material. Whereas, bixin was incorporated into the PCL nanofibers to bypass the gastrointestinal tract which can degrade orally administered drugs.

The electrospinning method was used to produce PCL and Bixin-loaded PCL sheets. After the designing of patch, the drug release was designed in two phases: an initial burst release followed by a sustained and gradual release over 14 days. To confirm the presence of Bixin in the PCL nanofibers sheet FTIR spectroscopy and X-ray diffractometry (XRD) was used. FTIR showed deeper valleys in the Bixin-loaded samples. Whereas, XRD provided additional evidence of successful drug incorporation.

The results demonstrated that Bixin-loaded PCL nanofibers significantly enhanced the wound healing process by as the drug releasae in first 10 hours which accelerated tissue regeneration across all healing phases. It also showed that a sustained release reaching 100% over 14 days. The results suggest that when PCL is combined with Bixin these patches offer a promising approach for

wound care.

Keywords: Transdermal Drug Delivery, Nanofiber, Wound Healing, Diabetes Mellitus.

Introduction

Diabetes mellitus is a chronic disease which impairs the body to produce insulin and losses its ability to regulate blood glucose levels (1) (2). Diabetes is caused by autoimmune destruction of pancreatic beta cells which results in insulin deficiency or insulin resistance (3). These pathophysiological disruptions affect glucose, lipid, and protein metabolism which cause metabolic imbalances. Sometimes it often involves both insufficient insulin secretion and reduced tissue responsiveness to insulin which further complicates the identification of hyperglycemia's root cause (2).

When hyperglycemia is not controlled it can be life threatening and lead to acute complications like hyperosmolar hyperglycemic states or diabetic ketoacidosis. When diabetes is not controlled its long-term complications include retinopathy, nephropathy, and foot ulcers. These complications may lead to amputation along with an increased risk of cardiovascular diseases, atherosclerosis, and cerebrovascular (4). Diabetes is broadly categorized into two main types: type 1 and type 2. Type 1 diabetes is an autoimmune disorder, involves the destruction of insulin-producing beta cells. Type 1 diabetes is typically diagnosed in children and young adults and can also occur when beta cells are damaged by disease or injury. The symptoms of Type 1 include polyuria, polydipsia, polyphagia, unexplained weight loss and fatigue (5).

Type 2 diabetes is characterized by insulin resistance which is commonly associated sedentary lifestyles and obesity. It develops gradually due to which early detection is difficult (6). Over the time many individuals experience macrovascular and microvascular complications. Although insulin production may be normal but still it remains insufficient to counteract the body's resistance to insulin (7). The symptoms of type 2 diabetes are similar to type 1 but with the addition of irritability, numbness in the extremities, slow wound healing, and frequent infections.

One of the most serious complications of diabetes in both types especially in individuals with neuropathy is diabetic foot ulcers. Neuropathy reduces sensation in the feet, allowing minor injuries to progress unnoticed into ulcers which are often complicated by poor circulation and an increased risk of infection (8).

According to the International Diabetes Federation (IDF) Diabetes Atlas (2021), there has been a marked increase in diabetes prevalence worldwide, with Pakistan experiencing one of the steepest rises (9). A statistical analysis shows that among 100 individuals, 49.10% are diabetic. Whereas, in Pakistan the prevalence of diabetic foot ulcer is 7.4%, Australia 1.5%, China 4.1%, the UK 6.3%, Iran 8.1%, the USA 13%, Canada 14.8%, and Belgium 16.6%. In addition to Pakistan, countries like China, India, and the United States also report high diabetes prevalence, indicating a global public health crisis (10), (11), shown in

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figure 1. Particularly, urban areas have seen a significant surge in diabetes cases due to lifestyle changes, dietary habits, and reduced physical activity. The given data shows the widespread nature of diabetes and its complications. It emphasizes the effective management and prevention strategies to reduce the complications of the disease (12), (9).

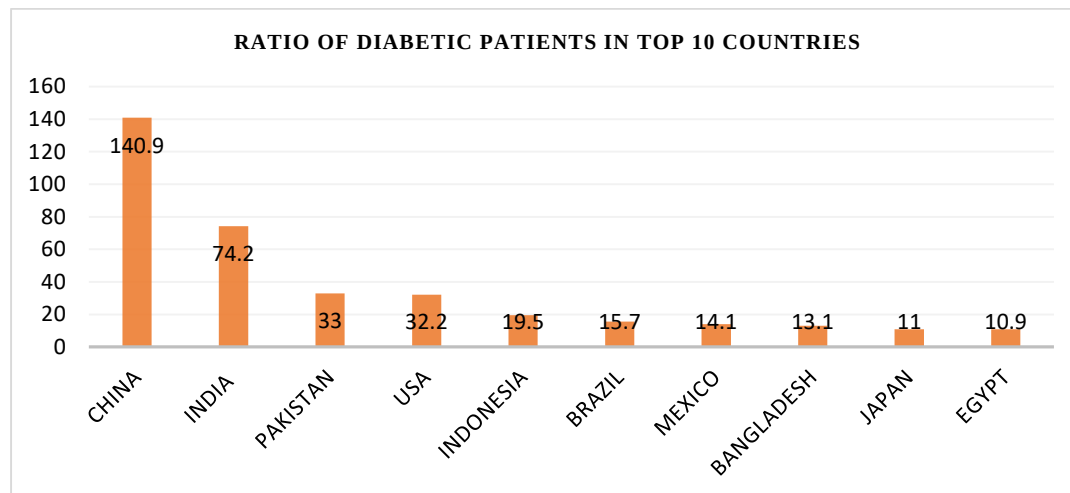


Figure 1 Statistical data of diabetic Patients

Diabetic wounds entail an efficient control and a multi-faceted solution. It requires high medical interventions and wound care. In medical treatments, special dressings are used to aid to keep a wet condition that is significant in conducive healing. On the one hand, anti-diabetic medications are important in maintaining the level of glucose in the blood which is also pertinent in wound management (13), (14). Along with oral medications, alternative therapeutic interventions such as transdermal drug delivery system (TDDS) have been looked upon because of their capacity to deliver drugs to the wound area (15). The TDDS provides an easy and painless method of delivering drugs into the body as compared to taking oral or injectable drugs. It entails microneedles and permeation enhancers that have enhanced infiltration capacity of drugs into the skin and into the bloodstream (16)(17). One of the most widely used forms of TDDS is transdermal patches which provide controlled doses of the drug over time in order to avoid systemic side effects and avoid first-pass hepatic metabolism. They are especially applied to such conditions that demand constant medication, including hormone replacement therapy and pain treatment (18), (9). Nanofibrous patches employed in TDDS are normally made up of several layers and each layer takes part in drug delivery. The structural support is achieved by the backing layer and the adhesive layer keeps the patch attached to the skin (19). The rate of drug release is controlled by a membrane area and the drug is stored in a form of a solution or a gel. The formulation is shielded by a liner, which is washed off prior to the use of the patch (2), (8). The stratified composition of these patches enables the controlled and sustained delivery of drug and is therefore a useful device in the management of diabetic wounds and

other illnesses that need delivery of drugs controlled.

Materials and Methods

The methodology involves development of PCL sheet and a Bixin-loaded PCL sheet. Both sheets were fabricated through a combination of stirring and electrospinning techniques. These are optimized for creating nanofibrous structures capable of effective drug release.

Materials

The following materials given in Table 1 were used in sheet formulations.

Table 1: Materials used for the Patch and its description

Material	Description
Polycaprolactone (PCL)	It is a biodegradable polymer with slow degradation which is mostly chosen for its suitability in drug delivery systems.
Dichloromethane (DCM)	It is a solvent used to dissolve PCL.
Methanol	It is an additional solvent used to assist in the formation of a homogeneous solution.
Bixin	It is a natural antioxidant. It is known for its wound healing properties.
Beta-cyclodextrin	It is used to enhance the solubility of Bixin.

Solution Preparation and Stirring

In the case of both of the sheets, this procedure started with the creation of 12 ml of a homogeneous solution of polymer. PCL dissolved in 5.4 ml DCM and 5.4 ml methanol (1.2 g) was dissolved in a clean bottle. In the case of Bixin-loaded sheet, 0.0036 g of Bixin and 0.001 g of beta-cyclodextrin were used in the same solution. To avoid the loss of solvent, particularly DCM, which is a highly volatile solvent, the bottle was capped with parafilm. The bottle was stirred by the use of a magnetic stir bar and the solution was stirred on a magnetic stirrer at room temperature during 3 hours. This was an important step towards the full dissolution of PCL as well as uniform distribution of Bixin and beta -cyclodextrin within the polymer matrix. Stirring will eliminate any chances of air bubbles or other solids which may adversely interfere with the electrospinning process.

Electrospinning

After the polymer solution was totally homogenous, it was loaded into two 3 ml syringes that had blunt needles. Both of the syringes were mounted in the

electrospinning and electrodes were added into them. The following parameters were set up in the machine:

The syringes were attached on the positive terminal (red crocodile wire) and the collector on the negative terminal (black crocodile wire).

The collector was positioned 12 cm away on the tips of the syringes, which is an important distance to ensure the proper fiber morphology.

In the case of pure PCL sheet the voltage was applied as 22 kV whereas in the case of Bixin-loaded sheet, voltage was changed to 26 kV to suit the varying viscosity and conductivity of Bixin-loaded solution.

The electrospinning was left to take 5 hours, and it was during this period that the solution of the polymer was converted into nanofibers. These fibers were deposited on the collector plate and as thin nanofibrous sheets provided in figure 2.

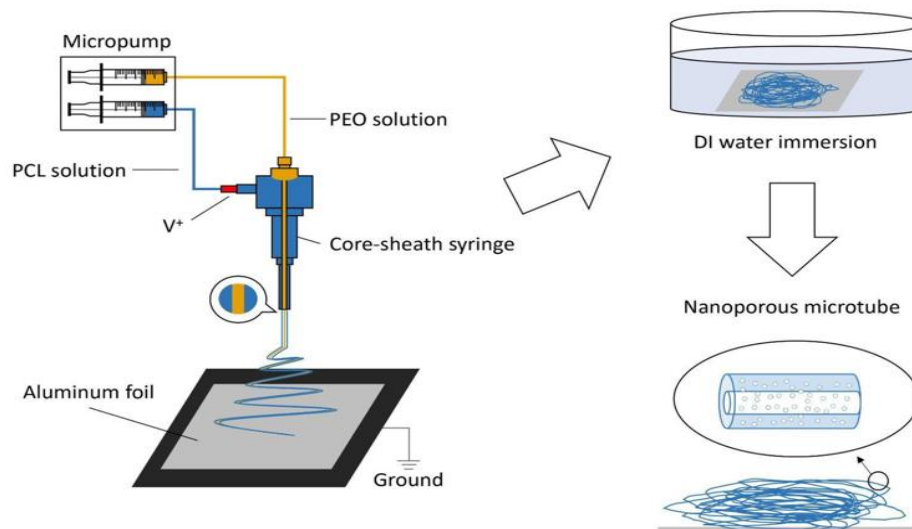


Figure 2 Electrospinning of Homogenous Solution

Results

The development of the nanofibrous transdermal patch started following a concept designing stage, which invested much effort on developing an effective delivery system of diabetic wound-healing medicine. This was primarily to make sure there was direct absorption of the drug to the skin and therefore it was not degraded in the gastrointestinal tract and first-pass metabolism of the drug was avoided. This type of delivery route preserves the therapeutic efficacy of the active compound which is especially useful in long-term diabetic patients who need long-term therapy.

FTIR Spectroscopy Analysis

Fourier Transform Infrared (FTIR) Spectroscopy was used to analyse the reaction between the polymer (PCL) and the drug molecule (Bixin) in the created nanofibers. Table 2 summarizes the results of pure PCL, pure Bixin and Bixin-incorporated PCL

membranes.

Table 2: Summary of FTIR Spectroscopy Results

Sample	Characteristic Peaks (cm ⁻¹)	Observation	Interpretation
Pure PCL	3000, 1700, 700–1500	C–H stretching and C=O vibrations	Represents typical polymer structure of PCL
Pure Bixin	1700, 1500	Peaks associated with conjugated double bonds	Indicates Bixin's distinct chemical structure
Bixin-loaded PCL	Similar peaks with deeper valleys at 1700, 1500	Deeper valleys due to presence of Bixin	Confirms successful incorporation of Bixin in nanofibers

Based on spectral results in Table 1, pure PCL had the intense absorption bands at approximately 3000 cm⁻¹, 1700 cm⁻¹ and in the 700-1500 cm⁻¹. These bands are related to the C-H stretching and the carbonyl (C=O) vibrations of the molecular structure of PCL. Pure Bixin, on the other hand, showed different points of peak at 1700 cm⁻¹, and 1500 cm⁻¹, which was linked to its conjugated double-bond system. Using Bixin and PCL to form the nanofibrous structure, the spectrum obtained with the mixture Bixin had the same peaks but stronger absorption valleys, especially at 1700 cm⁻¹ and 1500 cm⁻¹. This increased absorption bands prove that the Bixin has been molecularly interacted and entrapped successfully in the PCL matrix. Though these modifications were not so radical as to indicate the chemical modification of the polymer itself, it is clear that they are compatible with the other component. This compatibility is crucial to the development of a uniform and stable nanofibrous film that can retain and release drugs in the long run.

X-Ray Diffraction (XRD) Analysis

In order to confirm even more the incorporation of Bixin and its effect on the crystal structure of the PCL fibers, the X-Ray Diffraction analysis was performed. The results are given in Table 3.

Table 3: Summary of X-Ray Diffraction (XRD) Analysis

Sample	Crystallinity Observation	Change in Structure	Interpretation
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Pure PCL	Regular crystalline peaks observed	Stable polymer structure	Normal crystallinity of PCL
Bixin-loaded PCL	Modified diffraction pattern observed	Altered crystalline structure	Indicates molecular interaction between PCL and Bixin, confirming incorporation

As observed, pure PCL showed clear crystalline peaks which were typical of a stable polymer structure. Nevertheless, the pattern of diffraction in the Bixin-loaded PCL nanofibers had been altered and this indicates a partial disruption in the normal crystalline arrangement. This modification means that Bixin molecules are interacting with the polymer chains of PCL and this will affect the internal structure of the fibers. The occurrence of such change in the crystallinity is not only the proof of the successful inclusion of Bixin but can potentially increase the mechanical flexibility and overall functionality of the patch. Therefore, the FTIR analysis in combination with the XRD analysis is evidence of the successful incorporation of Bixin into the nanofibrous polymer network.

Drug Release Study

The drug release characteristics of the Bixin-loaded nanofibrous patch in-vitro is summarized in Table 4. The release profile was characterized by a two-phase release, a burst release phase followed by sustained release phase (after 10 hours) which showed that about 30-40 percent of released Bixin provided immediate therapeutic effect which was optimal in the early wound-healing response. After this time, it was released gradually but over a maximum of 14 days with almost 100 percent of the drug being released under control. This slow drug delivery is critical in providing the chronic diabetic wound with the sustained healing process necessitating constant availability of drugs.

The characteristic of the PCL nanofibrous system of a biphasic release profile indicates the ability of the system to offer rapid release and prolonged therapeutic benefits an essential requirement of an effective wound-healing patch.

Table 4: Drug Release Profile of Bixin-loaded PCL Nanofibers

Time Duration	Percentage of Drug Released	Release Phase	Description
0–10 hours	30–40%	Burst Release	Rapid initial release for immediate therapeutic effect

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10 hours–14 days	40–100%	Sustained Release	Gradual, controlled release ensuring prolonged drug availability
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Comparative Performance Evaluation

Table 5 presents a comparative study of plain PCL patch and Bixin-loaded PCL patch. The pure PCL membrane was used as a control to determine the impact of drug incorporation on different parameters.

Table 5: Comparative Evaluation of Patch Performance

Parameter	Pure PCL Patch	Bixin-loaded PCL Patch	Conclusion
Drug Presence	None	Confirmed via FTIR and XRD	Bixin successfully incorporated
Crystalline Behavior	Stable	Slightly modified	Indicates polymer-drug interaction
Drug Release	—	Two-phase (burst + sustained)	Suitable for controlled delivery
Wound Healing Efficacy	Normal	Enhanced tissue regeneration	Superior healing in Bixin-loaded patch

The comparison indicates that both FTIR and XRD data indicate that Bixin was successfully incorporated into the polymer matrix. The crystalline structure of PCL was slightly changed by the addition of the drug, which differs with the tendency to interact with the polymer and the active substance at the molecular

level. Furthermore, the patch loaded with Bixin also showed regulated dual-phase release and better healing effects in the experiments that were conducted, which confirmed the promotion of the tissue regeneration activity over the drug-free one.

Discussion

All the data provided in Tables 2-4 confirm the fact that Bixin was successfully integrated into the PCL nanofibrous matrix. The FTIR analysis demonstrates the compatibility of the chemical bonding interaction between Bixin and PCL, whereas the XRD analysis indicates that the inclusion of the drug did not change the crystallinity of the polymer greatly. The transdermal patch that is developed has a two-stage drug release profile which further substantiates the functionality of the transdermal patch. All these findings validate the use of this polymeric nanofibrous system as it is capable of retaining and releasing a therapeutic compound in the form of nanoparticles and preserving its structural integrity. These features provide the patch with a high potential to be used in wound management of diabetics, as it not only guarantees immediate and prolonged supply of the medication, but the patch does not lose its flexibility or durability. Further studies will be aimed at the optimization of Bixin concentration, measuring the mechanical and biocompatibility of the patch, and in vitro and in vivo experiments to prove the efficiency of the patch in clinical practice. The positive results of this study show that this nanofibrous transdermal system has huge potential as a new technique of treatment since the system is patient-friendly and can improve the wound healing in diabetic patients and reduce certain complications of wound healing including infection and slower healing time.

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