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POTENTIAL USE OF INSULIN PATCH TECHNOLOGY AS TRANSDERMAL DRUG DELIVERY IN EFFORTS TO TREAT DIABETES MELLITUS

POTENSI PENGGUNAAN TEKNOLOGI INSULIN PATCH SEBAGAI PENGHANTARAN OBAT TRANSDERMAL DALAM UPAYA PENGOBATAN DIABETES MELITUS

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ABSTRACT

Diabetes Mellitus (DM) in Indonesia continues to increase from 2013 to 2018. Diabetes Mellitus is associated with the production of the hormone insulin in the cells of the pancreas. An increase in blood sugar levels can stimulate insulin secretion. There are several ways to treat Diabetes Mellitus, namely by using drugs, herbal methods, and insulin injections. In addition, one of the DM treatments that can reduce pain is using insulin patch technology as a transdermal treatment. The manuscript for this publication was made to find out the potential of using insulin patch technology as transdermal drug delivery to treat DM. Using a literature review research method that discusses four focus studies, including 1) the structure of the pancreas gland, 2) the mechanism of insulin hormone production by the pancreas gland, 3) the causes, symptoms, and conditions of patients with DM, and 4) insulin patch technology as a transdermal drug in the treatment of diabetes. DM treatment efforts. In the Langerhans section of the pancreas, some cells function to produce the hormone insulin. The amino acids that make up insulin are encoded by exons formed in insulin cells. Some causes of DM namely genetics, age, the influence of food, lack of physical activity, and an unhealthy lifestyle. Some of the symptoms, namely polyuria, polydipsia, polyphagia, etc. Patients with DM need insulin intake to help balance blood sugar levels, one of which is by using an insulin patch in which there is a microneedle containing insulin n-vinylpyrrolidone (NVP) and the enzyme glucose oxidase. After a literature review, it can be concluded that the insulin patch has excellent potential and promise because during the study tested on rats and pigs obtained good results and was able to lower blood sugar levels, although development is still needed. The manuscript of this publication still has shortcomings, so the author suggested to the next author to be able to multiply the latest sources related to insulin patch. Through the creation of the publication, the manuscript realized that diabetes mellitus is a form of human negligence in maintaining the body that God has designed carefully and regularly.

Keywords: *diabetes mellitus, drug, insulin hormone, insulin patch, potency*

ABSTRAK

Diabetes Melitus di Indonesia terus mengalami peningkatan dari tahun 2013-2018. Diabetes Melitus berhubungan dengan produksi hormon insulin di sel β pankreas. Kenaikan kadar gula dalam darah yang meningkat dapat merangsang sekresi insulin. Beberapa cara pengobatan Diabetes Melitus, yaitu dengan penggunaan obat, metode herbal dan suntik insulin. Selain itu, salah satu pengobatan DM yang dapat mengurangi rasa sakit adalah menggunakan teknologi insulin patch sebagai pengobatan transdermal. Adapun naskah publikasi ini dibuat untuk dapat mengetahui potensi dari penggunaan teknologi insulin patch sebagai penghantaran obat transdermal dalam upaya pengobatan DM. Menggunakan metode penelitian kajian literatur yang membahas tentang 4 fokus kajian meliputi 1) Struktur kelenjar pankreas, 2) Mekanisme produksi hormon insulin oleh kelenjar pankreas, 3) Penyebab, gejala, dan kondisi pasien pengidap DM, dan 4) Teknologi insulin patch sebagai obat transdermal dalam upaya pengobatan DM. Pada bagian Langerhans pankreas terdapat sel β yang berfungsi untuk menghasilkan hormon insulin. Asam amino penyusun insulin dikodekan oleh ekson yang terbentuk di dalam sel insulin. Beberapa penyebab DM, yaitu genetik, usia, pengaruh makanan, kurangnya aktivitas fisik dan gaya hidup tidak sehat. Beberapa gejalanya, yaitu polyuria, polydipsia, polyphagia, dll. Pasien pengidap DM membutuhkan asupan insulin untuk dapat membantu menyeimbangkan kadar gula dalam darah salah satunya dengan menggunakan insulin patch yang di dalamnya terdapat jarum mikro yang berisikan insulin n-vinylpyrrolidone (NVP) dan enzim glukosa oksidase. Setelah dilakukan kajian literatur ternyata dapat disimpulkan bahwa insulin patch memiliki potensi yang sangat baik dan menjanjikan karena selama penelitian yang diujikan pada hewan tikus dan babi didapatkan hasil yang baik dan mampu menurunkan kadar gula dalam darah walaupun masih diperlukan pengembangan. Naskah publikasi ini masih memiliki kekurangan, sehingga penulis menyarankan kepada penulis selanjutnya untuk dapat memperbanyak sumber terbaru

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terkait insulin patch. Melalui pembuatan naskah publikasi ini menyadarkan bahwa penyakit Diabetes Melitus ini merupakan wujud kelalaian manusia dalam menjaga tubuh yang sudah Tuhan rancangkan dengan sangat teliti dan teratur.

Kata kunci: *diabetes melitus, hormon insulin, insulin patch, obat, potensi*

INTRODUCTION

Diabetes Mellitus has become a common disease found in the community. Diabetes Mellitus cases in Indonesia have continued to increase from 2013 to 2018 based on basic health research conducted in 2018. Indonesia is also in the seventh position as the country with the most diabetes cases globally and the highest prevalence of diabetes cases in Southeast Asia [1]. Based on the alarming number of Diabetes Mellitus cases and the importance of proper handling of Diabetes Mellitus, people with diabetes need appropriate therapy to prevent more serious complications from increasing the patient life expectancy [2].

Diabetes Mellitus is highly related to the mechanisms of the endocrine system. The endocrine system produces various types of hormones in the body [3]. Hormones are chemical substances produced from glands that will be released directly into the blood vessels. The imbalance of insulin production and sugar transport into cells causes Diabetes Mellitus [4].

Diabetes Mellitus is a group of symptoms that arise due to increased blood glucose levels due to a progressive decrease in insulin secretion [5]. Hyperglycemia is an early symptom of Diabetes Mellitus and is characterized by elevated blood sugar levels above 200 mg/dl [4]. Diabetes is also a metabolic disorder disease caused by a lack of the hormone insulin secreted by the pancreas or the body's ability not to use insulin from the pancreas effectively and causes hyperglycemia [6]. In addition, diabetes mellitus is a chronic disease associated with impaired immune function in the body, making it easier for patients to get infections [7].

Diabetes Mellitus is closely related to the normal glucose regulation system [8]. Increased blood glucose levels trigger the pancreas gland to secrete insulin. Excessive blood sugar levels damage the nerves, blood vessels, and other internal structures. Chronic hyperglycemia due to diabetes can result in long-term damage, impaired function, and failure of various organs such as blood vessels, heart, eyes, nerves, and kidneys [9].

Diabetes is divided into four categories [10]:

1. Diabetes Mellitus type 1: Insulin deficiency which is generally caused by the destruction of β −pancreatic cells.
2. Diabetes Mellitus type 2: Impaired insulin secretion that causes progressive insulin resistance.
3. Gestational Diabetes Mellitus: Only appears during pregnancy (diagnosed during the trimester stage of pregnancy).
4. Other specific types of diabetes: Monogenic diabetes syndrome, diseases of the exocrine pancreas, and the effects of drugs or chemicals (glucocorticoid use).

Diabetes Mellitus has various types of treatment; pharmacological and non-pharmacological approaches are alternative diabetes mellitus treatments [11]. Pharmacological approaches utilize drugs such as DMT1, insulin, sulfonylureas, thiazolidinediones, peptide analogs, meglitinide, biguanides, and others. Insulin therapy is done by injecting insulin into the patient continuously. While non-pharmacological include diet therapy, regular exercise, and making lifestyle changes was used to control diabetes [12]. Each treatment has its advantages and disadvantages. For instance, diabetic patients often feel impatient, bored, or exhausted when undergoing diet therapy, thereby not following the diet obediently [13]. Furthermore, insulin therapy performed pain and discomfort for DM patients and might be discontinued for therapy. Besides that, insulin pumps also tend to be expensive and must be replaced regularly, potentially increasing the risk of infection [14]. A transdermal therapy, such as insulin patch technology, is an alternative diabetes treatment with low pain levels.

Insulin patch technology holds great potential to assist diabetic patients in the process of treatment. However, insulin patches have not been marketed freely. This treatment method is still being researched in an effort to improve its quality. Therefore, this literature review investigated the potential use of insulin patch technology as a transdermal drug delivery system in Diabetes Mellitus treatment.

METHODS

The literature review method is a research method carried out for problem-solving based on an in-depth and critical study of existing literature materials relevant to the issues raised [15]. This study focuses on a literature review related to four main aspects, namely the: 1) structure of the pancreas gland, 2) mechanisms of insulin hormone production by the pancreas gland, 3) causes, symptoms, and conditions of pancreatic cells in patients with Diabetes Mellitus, and 4) insulin

patch technology as a transdermal drug delivery system in efforts to treat Diabetes Mellitus. This study uses various papers related to DM and the use of insulin patches. All the papers used were published in the last decade and some of the most complete and relevant references to the material covered. The papers used include national and international papers.

RESULTS AND DISCUSSION

Pancreatic gland structure. The pancreas gland is located near the duodenum at the back of the stomach [16]. The pancreas has two main tissues, namely acini, which produces enzymes that are useful for digestion. The second tissue was Langerhans Island, a network of islets resembling an island's shape as on the map [17] (Figure 1). The islets of Langerhans consist of clusters of cells scattered throughout the pancreas that make up 1-3% of the total weight of the pancreas [18]. The number of islets of Langerhans in the pancreas is about 1-2 million and has the largest size of 300µm and the smallest size in the range of 50 µm [19].

In carrying out its endocrine gland that produces hormones, the Langerhans islets are wrapped by a capsule consisting of connective tissue. A variety of hormone-producing cells useful for the body can be found on Langerhans Island. The first hormone-producing cells are α −pancreatic cells, which produce the hormone glucagon, which will later be used to break down glucose reserves stored in the liver to be carried to the blood. These cells also act to increase sugar levels in the blood, the number of these cells fulfills 25 % of the Langerhans islets [20]. β −pancreatic cells are useful for producing the hormone insulin. The β −pancreatic cells make up about 70% of the total area of Langerhans islets [21]. The hormone insulin helps lower glucose levels when there is too much in the blood. If the glucose level is still too high, excess glucose will be stored as a reserve in the liver to be later used for metabolic processes [22]. The morphology of the insulin hormone is green composed of oxygen, blue composed of nitrogen, red composed of carbon, and pink composed of sulfur [23]. The insulin structure can be seen in Figure 1.

In addition to these two cells, there are pancreatic F-cells (Gamma), pancreatic polypeptides are produced in these cells and are very small in size, accounting for 1% of the total Islets of Langerhans. These polypeptides are able to slow down the absorption of food [24]. The next cell is the Pancreatic Delta cell, where the hormone somatostatin is produced. Somatostatin inhibits the secretion of glucagon produced by the α−pancreatic cells, further inhibiting the excess production of polypeptides by the Pancreatic F-cells and the secretion of insulin produced by the β −pancreatic cells. The number of D-Pancreatic cells fills up 5% of the total area of the Island of Langerhans [23]. The pancreas gland also produces several hormones, such as gastrin and vasoactive intestinal peptide (VIP) [23].

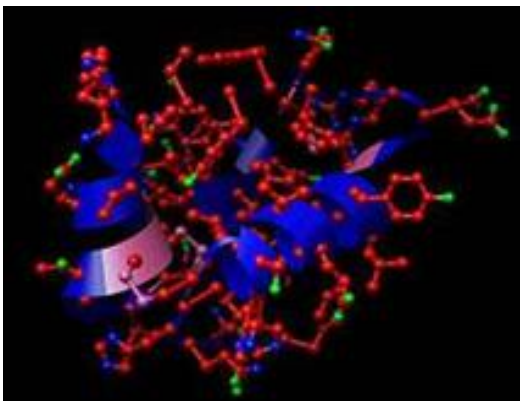

Figure 1. Structure of the hormone insulin [17]

Mechanisms of insulin produced by the pancreas gland. Insulin is an essential hormone that helps balance the body's metabolism. Insulin is a hormone that has two chains, including an A chain composed of 21 amino acids and a B chain composed of amino acids between two chains and linked by two disulfide bridges [25] (Figure 2). Insulin is produced when the body receives a signal of an increase in blood sugar levels. The picture below (Figure 2) is a picture of the insulin composing chain:

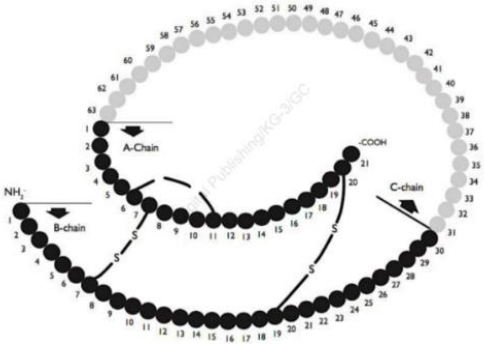

Figure 2. Insulin-composing chains [26]

In humans, insulin is located on a copy of the gene on chromosome 11 [27]. The insulin gene carried by humans has three exons. Exons are responsible for coding for amino acids [28]. Exons number one and two of the insulin gene code for the untranslated portion of the mRNA. Exon number two encodes a signal peptide (P). In exons 2 and 3, the B chain encodes the C peptide, while exon 3 encodes the A chain and adds it to the untranslated portion of the mRNA. The result of the first translation of the insulin gene is preproinsulin. Preproinsulin undergoes entry into the endoplasmic reticulum organelle. In these

organelles, preproinsulin undergoes protein breakdown (proteolytic) assisted by protease enzymes produced by proteolytic bacteria. The result of this process is proinsulin. Most proinsulins are arranged sequentially in which there are also prohormones that have been packaged in secretory granules. When the granule is ripe, it will contain insulin which has 51 amino acids with 21 amino acids in the A chain and 30 amino acids in the B chain, and there are also C-peptides [25].

When the body receives a signal that there is an increase in blood glucose levels, it stimulates insulin secretion in the pancreas. According to Merentek in Muhammad [29], insulin secretion depends on three factors, namely blood glucose levels, voltage-sensitive calcium channels in cells, and ATP-sensitive K channels. When blood glucose increases, metabolism increases, resulting in the increase of ATP generated from the glycolysis process, active transport of equivalents from the cytosol to the electron transport chain in mitochondria, and glucose oxidation in mitochondria [27]. Increased ATP/ADP can cause ATP-sensitive K+ channels to be blocked so that there will be depolarization of the plasma membrane. This process can cause voltage-gated Ca^{2+}-channels to open, allowing extracellular Ca^{2+} to enter and activate exocytosis of granules [27]. The process of cellular insulin secretion can be seen in Figure 3 below.

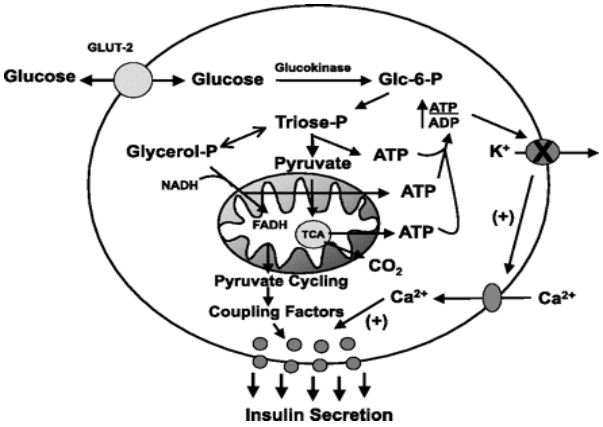

Figure 3. Cellular process of insulin secretion [27]

A picture that illustrates when insulin enters and the receptor opens can be seen in Figure 4 [30]. The performance of the insulin hormone plays an important role in maintaining the homeostasis of the body, especially in maintaining the balance of glucose levels in the blood. The attachment of insulin to the insulin receptor opens the glucose channel (Figure 4). When the glucose channel is open, excess glucose in the blood can enter the cells and be processed for storage in the form of glycogen [31]. Glycogen hormone will later be released by the pancreas to help the process of glucose synthesis [32]. When the process of insulin secretion is disturbed, it can cause Diabetes Mellitus [29].

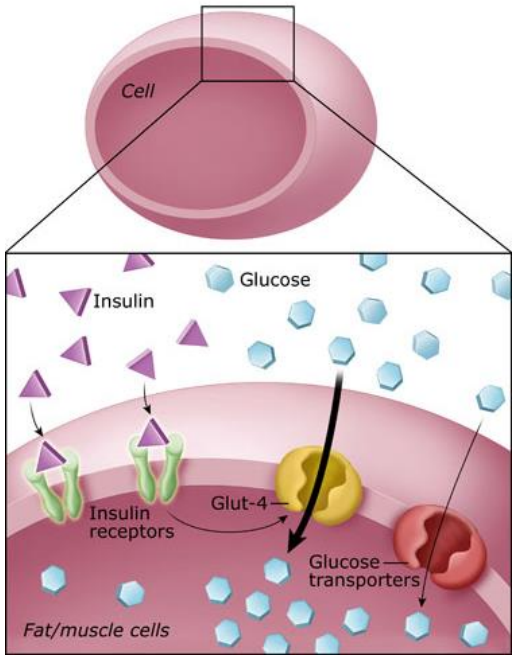

Figure 4. Insulin and receptors [30]

Causes, symptoms, and condition of β −pancreatic cells in patients with Diabetes Mellitus. Diabetes Mellitus is a disease that can arise due to heredity, age, food, resistance, physical activity, and the unhealthy lifestyle of sufferers [32]. One of the main causes of Diabetes Mellitus is a genetic factor or a family history of Diabetes Mellitus. Obesity can also be a factor in Diabetes Mellitus. Diabetes Mellitus is divided into two types, namely Diabetes Mellitus Type I and Diabetes Mellitus Type II. In addition, there is also a specific type of Diabetes Mellitus that occurs as a result of a genetic disorder in insulin action, disorders of the exocrine pancreas (e.g., cystic fibrosis), the effects of taking drugs or chemicals, and Diabetes Mellitus that occurs in women during pregnancy (gestational diabetes) [10]. Type II Diabetes Mellitus usually occurs due to a decrease in the amount of insulin produced by the pancreas [33].

According to Buraerah [12], the symptoms experienced by patients with Diabetes Mellitus can experience polyuria, polydipsia, polyphagia, tingling, and weight loss. In addition, patients with this disease also experience hyperglycemia and metabolic disorders of carbohydrates, proteins, and fats [11]. Another symptom is that the patient will experience dehydration and fatigue due to impaired utilization of CHO by the body [11]. Some even experience reduced vision, constipation, and candidiasis infection.

In the way insulin works in the pancreas of normal people and those with diabetes mellitus,

there are also differences which can be seen in Figure 6. A normal pancreas has normal β cells and can secrete the hormone insulin into the capillaries of blood vessels. Meanwhile, in the pancreas with type 1 diabetes mellitus, the β cells around the capillaries of the blood vessels have been damaged [37]. As a result, they cannot secrete the hormone insulin into the capillaries of the blood vessels [34] (Figure 5).

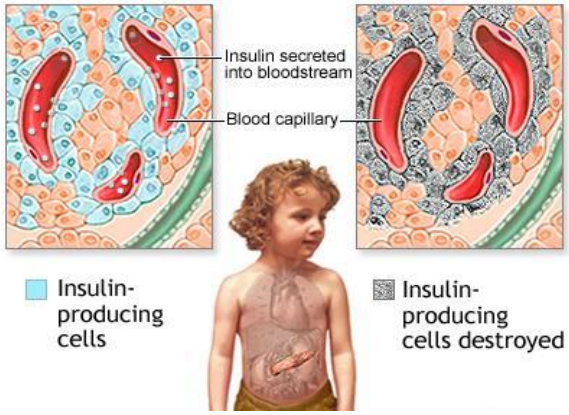

Figure 5. Comparison of β cells in a normal pancreas to β cells in the pancreas with Diabetes Mellitus type I [35]

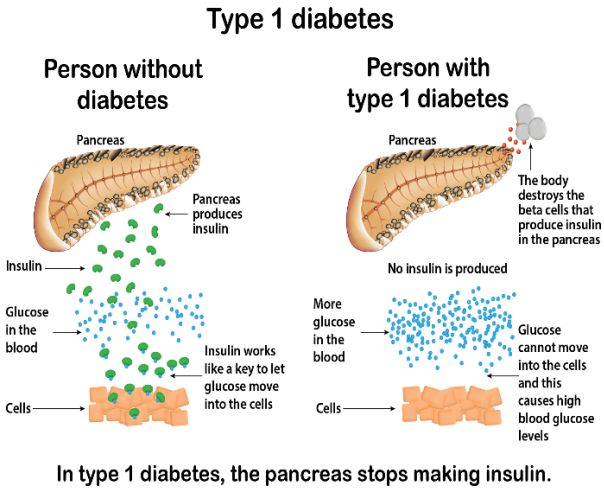

Figure 6. Differences between how insulin works in normal pancreas and pancreas with Diabetes Mellitus Type I [36]

In a normal pancreas, insulin is secreted into the blood vessels to help transport glucose into muscle cells or the liver (Figure 6). In the pancreas with Type 1 Diabetes Mellitus, insulin is not secreted, causing glucose to remain in the blood and contributing to high glucose concentration (Figure 6). As a result, blood glucose levels increase. The cells that do not receive glucose makes the body send a signal to produce more glucose, further increasing the concentration of glucose in the blood [38].

Insulin patch technology. A transdermal insulin patch is an adhesive device containing drug molecules. This device can be affixed to the skin surface to distribute the correct drug dose in the systemic channel every specific period [39]. Transdermal treatment with this type of patch must be thin, smooth, flexible, and homogeneous [40] so that the drug particles delivered through the stratum corneum are able to diffuse well through lipid molecules [41]. The insulin patch aims to provide painless insulin delivery to people with Diabetes Mellitus, a similar concept to the Transderm-Scop as a treatment for motion sickness and the nitroglycerin patch for the treatment of angina pectoris [42]. However, certain situations may arise during the transdermal treatment process. For instance, drug transport may be blocked by various skin chemical components, which usually have a larger size. Thus, microneedles were developed. The microneedle is designed to be short and thin, with a length of 50-900 µm and a diameter of 300 µm (Figure 7), allowing penetration into the nerves without causing pain [43].

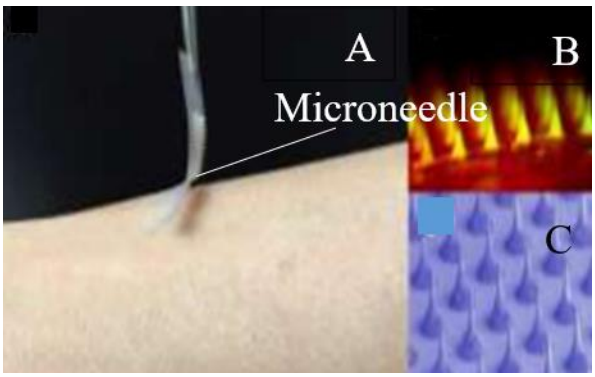

Figure 7. Insulin patch and microneedles A) insulin patch from the University of North Carolina/NC B) Magnified picture of a fluorescent microneedle patch C) Scanning Electronic Microscopy [16]

In one insulin patch measuring 6 mm, there are 121 microneedles with a height of 600 mm. Each microneedle contains insulin n-vinylpyrrolidone (NVP) with in-situ photopolymerization at 4°C and the enzyme glucose oxidase, surrounded by a polymer that dissolves at 29-30°C and NVP as a solvent [44]. This polymer consists of monomers released using Phototiade Array Detectors. These monomers are soluble when incubated in 2 ml phosphate buffer saline under purified microneedle conditions [44]. Glucose oxide works as a glucose sensor and polymer so that it becomes an actuator to release insulin [16]. Glucose oxide is an enzyme that has the function of transforming glucose become gluconic acid through the presence of oxygen [45]. The insulin core is incorporated into molecules assembled into vesicles like a combination of oil and water so that there are two

sides, namely hydrophobic and hydrophilic. The size of each molecule is 100 times smaller than the width of a human hair [44]. The insulin patch starts working when blood sugar levels increase as glucose fills the artificial vesicles, followed by the activity of the glucose oxidase enzyme that converts glucose into gluconate. This process requires a continuous supply of oxygen and often causes people with Diabetes Mellitus to experience mild hypoxia due to the transition of hydrophobic to hydrophilic 2-nitroimidazole molecules. As a result, the artificial vesicles start to fall apart and rapidly send insulin into the bloodstream [43]. This insulin release can also increase when glucose concentrations are increased from normoglycemic to hyperglycemic [44].

An in-situ polymerization process makes insulin patches under ultraviolet irradiation. Various monomers were formed by dissolving dimethylaminoethanol (DMAE) and 3-acrylamido PBA at a certain dose in NVP containing 0.5% mole of ethylene glycol dimethacrylate (EGDMA) that functions as a crosslinker and Irgacure 2959 that functions as a photoinitiator [44]. Then, insulin is directly dispersed into a monomer solution which will then be directly deposited with a pipette onto the surface of the microneedle mold [44]. For 10 minutes, the mold is placed under a vacuum to fill the microneedle mold by monomer. The excess solution in the mold must be waited until it disappears, after which the mold is placed under an ultraviolet lamp with a power of 100 W; 365 nm; black-ray. This process takes about 20 minutes at 4°C before Normal Optical Adhesive is added to allow the solution to solidify into the base of the patch under ultraviolet light for 10 minutes. After completing all of the steps, the insulin patch can be removed carefully and soaked for 2 hours in ethanol solution. Through this immersion, the unreacted monomer will be lost. The last step is to dry the insulin patch and store it in a closed container at room temperature [44]. The resulting micro needle is an anti-rust material and will fail or lose its function if it is bent [44].

The potential of insulin patch as a transdermal diabetes mellitus treatment is promising. The effect of drugs given through the skin is experienced faster than oral drugs or needle injections. Moreover, patients feel no pain when using the insulin patch [44]. In vivo research on insulin patches attached to rats injected with streptozotocin show that a 10 second application of the patches could help reduce blood glucose levels [44]. In a study that tested six-month-old mini pigs that had fasted for a full day and been induced by streptozotocin before being attached to the insulin patch, it was also proven that insulin patches helped balance glucose levels in the mini pigs. This adds to the potential for using insulin patches as a transdermal treatment in the future for the skin structure of mini pigs resembles the structure of human skin [43]. However, considering that the thickness of the stratum corneum is different in each individual, this research must be further investigated to create insulin patches with accurate doses released every specific period according to the needs of Diabetes Mellitus patients [43].

CONCLUSION

Insulin patch technology holds great potential to be utilized in treating Diabetes Mellitus as previous research that tested rats and mini pigs proved its effectiveness in reducing blood glucose levels. However, this treatment still needs to be further investigated and developed so that the right formula can be found and used in humans with different skin conditions.

The shortcomings of the publication manuscript that the author made were that several explanations were lacking in-depth due to the lack of supporting literary sources. Furthermore, writing the publication manuscript took only a limited amount of time. Suggestions for future publication manuscripts are to seek more recent sources regarding the development of insulin patch technology and to be more thorough in reviewing existing sources.

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