IJRAR.ORG E-ISSN: 2348-1269, P-ISSN: 2349-5138

INTERNATIONAL JOURNAL OF RESEARCH AND ANALYTICAL REVIEWS (IJRAR) | IJRAR.ORG

An International Open Access, Peer-reviewed, Refereed Journal

REVIEW ON: TRANSDERMAL MICRONEEDLES FOR INSULIN DELIVERY FOR THE TREATMENT OF DIABETES MELLITUS.

[1]Harleen Kaur ,[2]Manoj Kumar Katual,[3]Harshdeep Singh ,[4]Prabhjot

[1]Research Scholar,[2]Head of Department,[3]Research Scholar,[4]Research Scholar

[1]Rayat-Bahra Institute of Pharmacy, Bohan,Hoshiarpur

[1]Rayat-Bahra Institute of Pharmacy, Bohan,Hoshiarpur

ABSTRACT: Diabetes mellitus is a long-term metabolic disorder that arises due to insufficient pancreatic production of insulin or improper utilization of the insulin produced by the body. In light of this, diabetes treatment seeks to regulating blood glucose levels requires a variety of strategies, including frequent use of insulin therapy. Despite the several approaches that have been put out as substitute methods of administering insulin, subcutaneous injections remain the most often used method. In order to address the drawbacks associated with routine subcutaneous insulin injections and enhance patient adherence, the objective of this thesis was to create stable coated microneedles for fast transdermal delivery of insulin. In order to do that, commercial metallic microneedles and polymeric microneedles composed of biocompatible resin class I were researched in conjunction with 3D printing technology. The SEM showed that tiny layers formed on the microneedles without any insulin being lost in the coating process. Additionally, MicroCT demonstrated that the films adhered to the MNs' surfaces throughout the piercing. Different during the coating process, generate homogeneous coating layers, and enable quick release rates in order to address the issues with insulin instability. Raman and circular dichroism spectroscopy revealed that the majority of the carriers kept the native form of insulin's secondary structure in the films. Moreover, the insulin-carriers tended to form amorphous films, according to X-ray diffraction studies. Within 30 minutes, the Franz cell diffusion release assays demonstrated that the coated microneedles release insulin rapidly. Additionally, the research conducted on animals shown that the coated 3D printed microneedles facilitated a profile release that was comparable to the SC injections at first, followed by a longer prolonged release pattern for every insulin tested (glargine, aspart, and bovine)

I. INTRODUCTION

The chronic metabolic ailment known as diabetes mellitus is typified by elevated blood glucose levels. This condition arises from insufficient or inefficient insulin production by the body. Uncontrolled diabetes increases the risk of infection, blindness, gangrene in the lower limbs, and even amputation of the limbs. Since there is currently no cure, finding a safe and efficient medication for illness control is crucial in this regard. A balanced diet, frequent exercise, oral drugs, and, in many situations, a daily insulin injection are all part of the treatment (WHO, 1999, 2018). Like many medications, insulin has trouble penetrating the gastrointestinal tract due to enzymatic breakdown. While alternative administration routes were suggested (Jose et al. 2012; Veuillez et al. 2001; Hollander). The most popular substitute is the daily subcutaneous injection (Viswanathan, Muralidaran, and Raghavan 2017; Yaturu 2013, Chaudhury and Das 2011, and Yaturu 2007).Nevertheless, there are certain drawbacks to these hypodermic needles, including localized pain, allergies, lipodystrophy, hyperinsulinemia, needle phobia, anxiety, and trouble applying for elderly individuals (Kinesh et al. 2010; Ramaiya et al. 2018). Therefore, only molecules with a low molecular weight and lipophilicity can get through these barriers and enter the bloodstream (Bariya et al. 2012).The safe delivery of hydrophilic molecules and macromolecules remains a challenge, despite the extensive research conducted on various strategies to increase

skin permeability and create pathways large enough for molecules to pass through (Benson 2005; Paudel et al. 2010; Wu et al. 2019; Szunerits and Boukherroub 2018).

Many attempts have been undertaken to enhance insulin therapy and patient compliance as a result of the problems brought on by twice or three-day subcutaneous injections of insulin (Khafagy et al. 2007; Brunton 2008)The delivery of medications that are broken down in the gastrointestinal system, transdermal administration is a great option. However, the skin's barriers, particularly the stratum corneum and epidermis, restrict the amount of chemicals that can enter through that. Therefore, only molecules with a low molecular weight and lipophilicity can get through these barriers and enter the bloodstream (Bariya et al 2021) The safe delivery of hydrophilic molecules and macromolecules remains a challenge, despite the extensive research conducted on various strategies to increase skin permeability and create pathways large enough for molecules to pass through (Benson 2005; Paudel et al. 2010; Wu et al. 2019; Szunerits and Boukherroub 2018).Microneedles are an alternative transdermal delivery technology that has shown significant promise recently for the delivery of a variety of compounds via the skin, including insulin (Chen et al. 2016; Mahato 2017; Chen et al. 2015; Ross et al. 2015; Uddin et al. 2015). In order to allow the drug to bypass the stratum corneum layer of the epidermis and be absorbed systemically without stimulating nerves, microneedles are minimally invasive systems made up of micrometric needles included in the same array (Kim, Park, and Prausnitz 2012).

1.1 DIABETES.

According to its etiology, diabetes is a chronic illness that affects people globally. Type 1 and type 2 diabetes can be identified. Irreversible beta cell death in the pancreas, which is the cause of type 1 diabetes (formerly known as insulin-dependent or childhood-onset) is the hallmark of the condition. Insulin needs to be administered to the body on a daily basis due to inadequate production.

However, 90% of diabetes cases worldwide are type 2 diabetes, sometimes referred to as non-insulin-dependent or adultonset diabetes, which is typically characterized by the body's inefficient use of insulin. Excess body weight and physical inactivity are major risk factors for this type of diabetes. (WHO,1999.2013)The type 2 diabetes-related mismatch between insulin sensitivity and secretionillness as a heuristic to process a specific quantity of glucose. Nonetheless, as the β-cells gradually degrade, the generation of insulin is gradually reduced(Niswender2011)

.Regretfully, a six-year follow-up, people with type 2 diabetes will need insulin therapy (Wrightetal.2002). In both situations, hyperglycaemia is a typical side effect of uncontrolled diabetes that can eventually cause major harm to a number of body systems, including the heart, blood vessels, kidneys, eyes, and nerves, all of which can have an adverse effect on a patient's quality of life (WHO, 1999; 2018). Afterwards, a balanced diet, consistent exercise, oral therapy, and frequent physical drugs, and frequently, daily insulin injections, which will completely postpone or even eliminate those consequences. (American diabetes association 2010). According to studies, diabetes, which affects millions of people globally, is one of the diseases with the greatest rate of growth in recent years. In its eighth edition of the IDF Diabetes Atlas (2017), the International Diabetes Federation (IDF) stated that 425 million people worldwide, ages 20 to 79, are thought to have diabetes. 30.2 million of those are in the US, 12.5 million are in Brazil, and 2.7 million are in the UK.

1.2 SKIN STRUCTURE

The skin is one of the most vital organs in the body, accounting for 10% of the total body mass in adults and having an average surface area of 2 m2. It is responsible for many vital processes, such as hormone synthesis, thermoregulation, sensory perception, barrier protection against exogenous substances, and bodily hydration maintenance(Barry2007;Waugh,Anne;Grant2014). The human skin is composed of three primary layers, each with unique properties, as well as a few appendages that provide aqueous channels into the skin, such as sweat glands, sebaceous glands, and hair follicles (Figure 1.1). According to HAE Benson (2012), the epidermis is the outermost layer that is revealed, followed by the dermis and the hypodermis, which is the innermost layer.

EPIDERMIS

The stratum corneum and the other four different layers of stratified squamous epithelium make up the 150-200µm thick epidermis. These layers include the stratum Basale or germinativum at the bottom, the stratum lucidum, the stratum granulosum, and the stratum spinosum. The epidermis gets all of its nourishment through passive diffusion through the interstitial fluid because, except from these layers, it lacks a vascular network (Bruno, Miller, and Lim 2013).

The three most prevalent types of cells found in the epidermis are melanocytes, keratinocytes, and Langerhans cells. The first ones are the primary epidermal cells, which divide by going through mitosis at the stratum germinativum, where they cling to hemidesmosomes. The newly formed cells gradually move in the direction of the epidermis' surface while the fibrous protein keratin takes the place of the cytoplasm to produce the stratum corneum(Alkilani,McCrudden,andDonnelly2015).

In the deep germinative layer, melanocytes synthesize the pigment melanin, which is absorbed by the keratinocytes, the surrounding epithelial cells, and offers protection from ultraviolet light. The quantity of melanin in the skin determines skin colour, although the amount produced varies depending on an individual's genetic makeup and environmental stimuli. Melanin is created to protect skin in proportion to the amount of sunshine that it receives (Waugh, Anne; Grant 2014).

STRATUM CORNEUM

The stratum corneum is primarily in charge of the skin's effective physical barrier. It is composed of ten to thirty layers(10–20µm) of mature keratinocytes known as corneocytes, which are mostly made of keratin and, to a lesser extent, lipid, enclosed in a lipid extracellular matrix and housed in a cornified cell envelope (Marwah et al. 2017). Drug administration through the skin has been investigated despite this effective physical barrier. Active molecules can be applied topically to the skin in dermatological formulations like makeup and bug repellents. When they are in a topical formulation, they can also be absorbed systemically when intended for transdermal distribution, which is a great way to administer them. They can also be transported into deeper regions of the skin medications that the gastrointestinal tract breaks down (Bariya et al. 2012; Benson 2012).

DERMIS

The skin's dermis is a fibrous network of tissue that gives it resilience and structure. It is made up of a connective tissue matrix that is roughly 3-5 mm thick and primarily consisting of fibrous proteins and mucopolysaccharide (Barry2007). Numerous specialized cells and structures are also present in the dermis. Fibroblasts, macrophages, and mast cells are the predominant cell types found there, while sweat glands, sebaceous glands, hairs, sensory nerve endings, and a well-developed capillary system are the primary anatomical features (Waugh, Anne; Grant 2014).

1.3 SKIN AS A SITE OF DRUG DELIVERY

Molecules can traverse the epidermis in three different ways after coming into contact with the skin's surface: via sweat ducts, via appendageal routes (hair follicles and sebaceous glands), or through the stratum corneum (Figure 1.2). The majority of chemicals penetrate the skin by a combination of these pathways, with the continuous stratum corneum serving as the main route of penetration. Moreover, only 0.1% of the appendage's fractional area is available for absorption. According to Benson (2012), passive absorption (diffusion) through transcellular or intercellular pathways within the cells causes the stratum corneum to permeate. The molecules in a transcellular diffusion must get beyond the interleaving lipids and corneocytes. Because of this, the molecules must be hydrophobic because of the intercellular lipid matrix and eighter hydrophilic because of the high concentration of keratin inside the corneocytes. In contrast, for molecules to diffuse and partition through the intercellular lipid matrix through the intercellular pathway, they must have hydrophobic characteristics (Benson 2012). Then, according to Barya et al. (2012).

1.4 Insulin.

The pancreatic β-cells secrete insulin, an anabolic hormone that facilitates the uptake of glucose, free fatty acids, and amino acids into muscle, liver, and adipose tissue. Because it is necessary for survival, this hormone affects how all macronutrients are stored (Niswender 2011). With a molecular weight of 5800 Daltons, insulin is a tiny, globular protein composed of two peptide chains, A and B, connected by two disulfide links. With two α-helix portions and 21 residues of amino acids, the A chain is quite compact. With 30 amino acid residues and a greater portion of the alpha helix, the B-chain wraps around the A chain (Sluzky and Langer

1992; Ortiz et al. 2004). Within the first half-century following its discovery, insulin was isolated and refined from the pancreas of pigs and cows. Human insulin wasn't commercially available for therapeutic use until the 1980s, when recombinant DNA techniques were developed (Bethel & Feinglos (2005). The first structure (the backbone) of human, porcine, and bovine insulins differ from one another. Bovine insulin differs by three amino acids at residues A8, A10, and B30, whereas porcine insulin differs by only one amino acid at residue B30. (Ortiz and associates, 2004).

Numerous strategies have been investigated to enhance insulin therapy and get it closer to the physiological insulin profile since human insulin was first obtained using recombinant DNA (Melo et al. 2019). In healthy people, there are two stages to the secretion of insulin. 1) In a bolus, when insulin concentration rises sharply in reaction to meal consumption; and 2) At a basal rate, which is constantly released at low levels in response to the liver's endogenous synthesis of glucose (Niswender 2011). Numerous insulin analogs were proposed for both the basal and bolus phases of the insulin treatment protocol, which aims to imitate the natural rhythm of insulin secretion in order to regulate appropriate blood glucose level. (Feinglos and Bethel, 2005). As a result, insulin preparations are available in two forms: intermediate (NPH) and long-acting (glargine and detemir) to replace basal insulin production and short-acting insulin (regular, lispro, and as part) for use in bolus therapy (Waller and Sampson 2018).

1.5 TRANSDERMAL DELIVERY SYSTEMS

For medications like big, hydrophilic proteins that are difficult to penetrate the gastrointestinal tract or are subject to enzymatic degradation, transdermal drug delivery devices (TDDS) offer an appealing alternative route. According to Alexander et al. (2012), those systems are made to get beyond the stratum corneum barrier and deliver the medication into the viable epidermis or dermis for systemic absorption without injuring the deeper tissues or triggering nerves.

The physical-chemical properties of the drug in the formulation (partition coefficient, molecular size, and solubility), the characteristics of the skin (if intact, age and site, degree of hydration, and skin temperature), and, lastly, the application area, if any pre-treatment is necessary, are the main determinants of a therapeutic drug delivery system's efficacy skin preparation and the duration of the formulation's interaction with the skin (Alexander et al. 2012).To increase skin permeability and maker spaces large enough for molecules go through it According to their methodology and physical-chemical characteristics, a variety of tactics, from chemical to physical procedures, have been investigated (Benson 2005; Paudel et al. 2010; Chen et al. 2009; Bolhassani 2019; Patel, Cholkar and Mitra 2014).

Langer and Prausnitz (2008) have classified the TDDS into 3 different generations:

First generation TDDS.

Transdermal patches, which are essentially an adhesive to be applied to the skin and allow the medicine to be stored there or in a reservoir made typically of a particular membrane, are an example of the first generation of TDDS. help regulate the medication's skin-transmitted release. Metered liquid sprays, gels, and other topical formulations were created to be administered to the skin in addition to those patches. Furthermore, passive diffusion alone through these systems may deliver most tiny lipophilic and powerful medicines in the therapeutic range. Although stratum corneum acts as a barrier to the first-generation transdermal distribution technique, numerous items utilized for therapeutic applications are currently available on the market, such as patches for nitro-glycerine, scopolamine, among many others, lidocaine, testosterone, estrogen, and nicotine (Al-Hanbali et al. 2019).

Second generation TDDS.

Iontophoresis, non-cavitational ultrasound, and traditional chemical enhancers are all part of the second generation of TDDS. All techniques created in this generation are essentially driven by the need to improve skin permeability and application of an externally powered force to carry the medication through the skin. Along with liposomes, dendrimers, microemulsions, and prodrugs, the most often employed chemical enhancers for transdermal administration include solvents and surfactants. Among the physical techniques, non-cavitational ultrasound uses an oscillating pressure wave to disrupt the stratum corneum lipid structure and increase drug permeability.

Third generation TDDS.

The goal of more severely disrupting the stratum corneum, the third generation of TDDS uses methods such as combining chemical enhancers, biochemical enhancers, Electroporation micro-poration(thermal ablation, laser ablation, and microneedles, microdermabrasion using pressured particles and sandpaper, and cavitational ultrasound (Prausnitz and Langer 2008; Paudel et al. 2010).

1.6 COMBINATIONS OF CHEMICAL ENHANCERS.

Chemical enhancers are compounds that change the stratum corneum's lipid structure, improving the permeability of the layer so that molecules can pass through it and facilitating transdermal drug administration. Despite the existence of multiple component categories, the delivery of high-molecular-weight molecules remains a difficulty and skin irritation a serious issue. In order to get around those problems, certain mixes of chemical enhancers at low concentrations and particular ratios can demonstrate strong penetration with comparatively little discomfort (Karande, Jain, & Mitragotri, 2004).

Enhancers biochemicals Peptides, which interact with the skin through various pathways, are utilized as biochemical enhancers to improve skin permeability by increasing the amount of medication. that are able to cross the stratum corneum (Kim, Ludovice, & Prusnitz, 2007; Li et al., 2008; Rothbard et al., 2000; Y. Chen et al., 2006). According to a study, they can occasionally work far better when paired with a chemical enhancer (Kim et al., 2007).

CAVITATIONAL ULTRASOUND.

Low-frequency cavitation bubbles created by ultrasonic application on skin have the potential to damage the stratum corneum's structure and enhance skin permeability. It is well known that low-frequency ultrasonography can produce water channels inside the lipid bilayers are created by microbubbles in the water and tissue that collapse (Baris E. Polat1, Douglas Hart2, Robert Langer1, 2011; Smith, 2007).

ELECTROPORATION.

Through the temporary rupture of the stratum corneum's structure caused by high-voltage electrical pulses applied to the skin for a few milliseconds, electroporation enables the movement of both big and small molecules that would not otherwise be able to penetrate in any way (Ita 2016; Denet, Vanbever, and Gale 2004).

MICRODERMABRASION.

Pressurized particles, like sodium chloride or alumina, are used in microdermabrasion to eliminate the stratum corneum and promote skin permeability. Sandpaper can be used to get a similar result. Even though it was created in the 1980s for use in cosmetic operations to lessen wrinkles, tattoos, and superficial scars additionally fine lines, a number of studies have demonstrated thatmicrodermabrasion is an efficient way to boost low molecular weight chemical transdermal distribution (Fujimoto, Shirakami, and Tojo 2005; Andrews et al. 2011).

MICROPORATION.

The process of microporation entails making tiny holes in the skin to allow water-soluble and macromolecules to pass through. The formation of microchannels in the skin can be achieved by thermal, radiofrequency, or laser ablation by subjecting it to brief, high-temperature pulses that can remove the stratum corneum and create structural disruption without severely scorching or harming the deeper tissues. However, by creating a passage in the skin, microneedles generate such channels (Banga, 2009).

1.7 MICRONEEDLES.

Microneedles, which combine hypodermic and transdermal patches, are seen of as a hybrid approach. They consist of micrometric needles arranged in an array, and depending on their size, they can puncture the epidermis and stratum corneum without activating neurons, though (Donnelly, Raj Singh, and Woolfson 2010; Tuan-Mahmood et al. 2013).These systems, which can be made of a variety of materials (metals, polymers, silicon, ceramic) and techniques (infrared laser, lithography, micromolds, electroplating, etching), are a promising method of drug delivery that is independent of the drugs' size or lipophilicity (Mcallister et al., 2003, Tuan-Mahmood et al., 2013; van der Maaden, Bouwstra, 2012). Generally speaking,

MN can be divided into five categories: hydrogel-forming MN, poke-and-patch, coat-and-poke, poke-and-release, and poke-and-flow.

POKE-AND-PATCH.

The poke and patch method involves pre-piercing the skin using solid microneedle arrays to generate microchannels that are then used to apply a transdermal patch or a traditional medication formulation.travel in a passive manner via these microchannels. However, according to (Tuan Mahmood et al. (2013),

COAT-AND-POKE.

The "coat and poke" method uses solid microneedles coated in a medication or vaccination formulation. The formulation is pushed into the skin and then Drug discharged and dissolved. Avoiding the heating process is the main benefit (Vrdoljak et al.

2012; Harvinder S. Gill and Prausnitz 2007). These coated MNs have been utilized to penetrate the skin and provide DNA, proteins, and peptides, as well as vaccinations. (Qiu et al. 2012; Larrañeta et al. 2016).

POKE-AND-RELEASE.

Dissolvable microneedles, such as those composed of sugars, polysaccharides, or synthetic polymers, are the subject of Poke and Release. Research has demonstrated that those MN may be used to provide a variety of of various materials, such as vaccinations (Matsuo et al., 2012; Wu, 2013) and insulin (Ito et al., 2012; Liu et al., 2012; M.-H. Ling and Chen, 2013). Iontophoresis has also been employed with them (Garland et al. 2012).

POKE-AND-FLOW.

Hollow MN of various materials, including silicon, metal, hollow glass, polymers, and ceramics, is associated with poke and flow. Each microneedle, as the name implies, has a hollow interior that allows molecules to be transferred to the inner layer of the skin. A convective drug flow is delivered into deeper skin layers by the conical shape of the microneedles, which also feature a conical interior cavity (Xie, Li, and Yu 2015; Lhernould, Deleers, and Delchambre 2015).

HYDROGEL-FORMING MN.

Last but not least, MN composed of polymers such hyaluronic acid, agarose, chitosan, polyvinyl alcohol, and many more substances that show the ability to swell in water and retain a sizable amount of water inside the buildings. A patch carrying the medication is fast diffused through the enlarged microprojections and is attached to the baseplate of the array (Donnelly et al. 2012; Hong et al. 2014). They are also readily sterilised and come in a variety of patch sizes and geometries. Additionally, according to Donnelly et al. (2012), Donnelly et al. (2014), Banga (2009), and McCrudden, Alkilani, Courtenay, et al. (2014) Despite the development of numerous MNs techniques, the most effective penetrating properties are typically provided by solid MNs, mostly as a result of the inherent properties of the applied materials; nevertheless, the majority of them have labour-intensive, multi-step fabrication processes that can restrict the ability to scale up production. In this regard, 3D printed microneedles may be an intriguing method for quickly producing solid MNs with favourable mechanical characteristics.

1.7 3D Printed Microneedles.

3D printing is a family of different techniques that apply a computer model design to create physical three-dimensional objects. The main technologies that have or are expected to present the most promising contribution in the field of transdermal drug delivery, more specifically with microneedles

1.8 FUSED DEPOSITION MODELLING (FDM).

Fused Deposition Modelling (FDM): One of the most popular 3D printing methods is called FDM, and it works by heating thermoplastic polymers in the form of filaments and then depositing the semi-melted material in thin strands layer by layer (Park et al. 2018). This process is known as melt-extrusion.While this technology has shown promise in the pharmaceutical industry for drug delivery (Goyanes, Chang, et al. 2015; Sadia et al. 2016; Alhijjaj, Belton, and Qi 2016), it is still difficult to resolve complex microstructures and cannot be effectively used to fabricate MNs (Economidou, Lamprou, and Douroumis 2018; Low et al. 2017).

Photopolymerization-based technologies: Technologies based on photopolymerization make use of photopolymer resin that, when stimulated by a laser, selectively polymerizes to harden or cure it. In this group, digital light (DL), stereolithography (SLA), and two-photon polymerization (2PP) are the most promising technologies for applications involving microneedles. handling (DLP).

Two-Photon polymerisation (2PP): The two-photon polymerisation (2PP) also uses photo-sensitive polymers with, however, a near-infrared laser with ultrashort pulses. In this case, the laser beam focus on local points volumes which is solidified by two-photon absorption. The main advantage of this technology is the capability of production of elaborate and complex structures in the micro and nanoscale (Gittard et al. 2010; Lee et al. 2008; Zhou, Hou and Lin 2015). Although 2PP allows the manufacture of structures with small details, the technology still very expensive and the large industrial production of MNs could be a challenge.

Stereolithography and Digital Light Processing: The first solid freeform fabrication method to be made commercially available was SLA, which was created in the 1980s. With the use of a UV laser beam, the liquid resin in a reservoir is solidified layer by layer in this additive manufacturing method.

While DLP is an advancement of SLA technology, it prints the entire layer at once considerably more quickly than SLA due to the use of a projector laser rather than a laser beam (Figure 1.7) (Economidou, Lamprou, and Douroumis 2018).While both techniques operate on the same idea, the SLA method uses a laser beam to solidify the resin, creating rounded lines along the way, while the DLP method uses a digital projector screen to flash a single image of each layer across the object's whole cross-section While DLP has the benefit of shorter print times, printing small and detailed items is difficult because of its fixed number of pixels and resolution dependence on the projector. In this way once SLA printers are an excellent choice for transdermal distribution applications and the production of microneedles since they are independent of the projector's resolution and can print small structures at a high resolution. Just a small number of biocompatible resins are available for stereolithography out of all the materials that can be used for 3D printing. Dental SG resin is a Class I biocompatible resin that has been approved by the FDA (EN-ISO 10993-1:2009/AC:2010, USP Class VI) and is used in dentistry. It has a high mechanical strength and may be effectively used to fabricate microneedles (Pere and colleagues, 2018).

All things considered, 3D printing is a promising method for fabricating MNs that gets over many of the restrictions and disadvantages of existing approaches, including expensive equipment, several intricate step procedures, time-consuming, and challenging to scale up.

1.9 MICRONEEDLES FOR INSULIN DELIVERY.

A number of coated and polymeric microneedles have recently been employed to apply a variety of medications topically in a single step (Katsumi et al., 2012; McCrudden, Alkilani, Cian M. McCrudden, et al., 2014; McGrath et al. However, only a small number of investigations have been conducted using insulin (Ito et al. 2006; Ito et al. 2012; Liu et al. 2012; Ling and Chen 2013; Lahiji, Dangol, and Jung 2015).

According to a study, the amount of insulin inserted into the microneedle that dissolves can simply regulate how much of a hypoglycemic response occurs. Liu et al. (2012) created an insulin-loaded microneedles array in this study utilizing no organic solvents or a heating step in the manufacturing process. They discovered that after an hour, the hyaluronic acid microneedles created via the micromolding procedure completely disintegrated and released the insulin. An additional biodegradable microneedle patch was created for the rapid release of insulin in the skin's interstitial fluid. It was created using a micromolding technique using 3-aminophenyl boronic acid-modified alginate and hyaluronate. However, the MNs required twice as long (2 hours) for the same SC injection dose in order to achieve the minimal blood glucose level (Yu, Jiang, Zhang, et al. 2017).

For quick release of insulin, Ling and Chen (2013) created dissolvable MNs made of starch and gelatin. The results of the study demonstrated that such polymeric microneedles could release the encapsulated insulin in addition to improving insulin stability. The Microlancer is a patchless dissolving microneedle that was introduced by Lahiji et al. in 2015. They suggested using a device to introduce the needles of a carboxymethyl cellulose microneedle filled with insulin into the skin. Additionally, they compared the outcomes of the in vivo administration and insulin release profile using the corresponding SC injection and microneedles patch. They observed that the Microlancer insulin release, which achieved the minimal blood glucose level in three hours, was far more successful than its corresponding microneedle patch. Insulin has a 90% relative bioavailability and is absorbed into the skin in less than two hours (M.-H. Ling and Chen 2013).

Despite the encouraging results of those investigations, the majority of polymeric materials employed in dissolvable MNs are not readily suited for rapid transdermal distribution because of their slow-degrading nature. However, they are appropriate for sustained drug delivery (Liu et al. 2012; Xie, Li and Yu 2015).

1.10 KEY OBJECTIVES OF THE RESEARCH.

The goal of this study was to create coated microneedles for quick transdermal insulin delivery by: 1) determining ratios of stable aqueous polymeric and sweet insulin formulations for inkjet printing microneedle coating, 2) utilizing the stereolithography technique to develop 3D printed microneedles;3) optimizing coating formulations onto metallic and 3D printed MNs in accordance with the necessary dose;4) assessing the MNs' in vitro release of insulin; and5) assessing the in vivo release of the optimal coated MNs system.

1.11 REFERENCES.

- Al-Hanbali, O.A., Khan, H.M.S., Sarfraz, M., Arafat, M., Ljaz, S. and Hammed, A. (2019). Transdermal patches: Design and current approaches to painless drug delivery. Acta Pharmaceutica, 69
- Alexander, A., Dwivedi, S., Ajazuddin, Giri, T.K., Saraf, Swarnlata, Saraf, Shailendra and Tripathi, D.K. (2012). Approaches for breaking the barriers of drug permeation through transdermal drug delivery. Journal of Controlled Release,
- Alhijjaj, M., Belton, P. and Qi, S. (2016). An investigation into the use of polymer blends to improve the printability of and regulate drug release from pharmaceutical solid dispersions prepared via fused deposition modeling (FDM) 3D printing. European Journal of Pharmaceutics and Biopharmaceutics,
- Alkilani, A.Z., McCrudden, M.T.C. and Donnelly, R.F. (2015). Transdermal drug delivery: Innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics,
- Allison, S.D., Chang, B., Randolph, T.W. and Carpenter, J.F. (1999). Hydrogen Bonding between Sugar and Protein Is Responsible for Inhibition of Dehydration Induced Protein Unfolding.
- Archives of Biochemistry and Biophysics, 365(2), 289–298.Altamimi, M.A. and Neau, S.H. (2017). Investigation of the in vitro performance difference of drug-Soluplus® and drug-PEG 6000 dispersions when prepared using spray drying or lyophilization. Saudi Pharmaceutical Journal,
- Ameri, M., Kadkhodayan, M., Nguyen, J., Bravo, J.A., Su, R., Chan, K., Samiee, A. and Daddona, P.E. (2014). Human growth hormone delivery with a microneedle transdermal system: Preclinical formulation, stability, delivery and PK of therapeutically relevant doses. Pharmaceutics,
- American Diabetes Association (2010). Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 33(Suppler 1), pp. S62–S69.
- Andrews, S.N., Zarnitsyn, V., Bondy, B. and Prausnitz, M.R. (2011). Optimization of microdermabrasion for controlled removal of stratum corneum. International Journal of Pharmaceutics,
- Anselmo, A.C., Gokarn, Y. and Mitragotri, S. (2018). Non-invasive delivery strategies for biologics. Nature Reviews Drug Discovery,
- Arafa, M.F., El-Gizawy, S.A., Osman, M.A. and El Maghraby, G.M. (2016). Xylitol s a potential co-crystal co-former for enhancing dissolution rate of felodipine: preparation and evaluation of sublingual tablets. Pharmaceutical Development and Technology,
- Banga, A.K. (2009). Microporation applications for enhancing drug delivery. Expert opinion on drug delivery, 6(4), 343–354 Bariya, S.H., Gohel, M.C., Mehta, T.A. and Sharma, O.P. (2012). Microneedles: an emerging transdermal drug delivery system. Journal of Pharmacy and Pharmacology,
- BASF(n.d.).Soluplus®.[Online].Available fromhttps://industries.basf.com/bin/bws/documentDownload.en.8805242743253 [Accessed 3 March 2019]Benson, H. (2012). Skin Structure, Function, and Permeation In: A. C. Benson, H. E; Watkinson, ed. Transdermal and Topical Drug Delivery: Principles and Practice, pp.448.Benson, H. (2005). Transdermal Drug Delivery: Penetration Enhancement Techniques. Current Drug Delivery, 2(1), 23–33.Bethel, M.A. and Feinglos, M.N. (2005). Basal insulin therapy in type 2 diabetes. The Journal of the American Board of Family Practice,
- Boehm, R.D., Miller, P.R., Schell, W.A., Perfect, J.R. and Narayan, R.J. (2013). Inkjet printing of amphotericin B onto biodegradable microneedles using piezoelectric inkjet printing.
- Bruno, B.J., Miller, G.D. and Lim, C.S. (2013). Basics and recent advances in peptide and protein drug delivery. Therapeutic Delivery,
- Brunton, S. (2008). Insulin delivery systems: reducing barriers to insulin therapy and advancing diabetes mellitus treatment. The American journal of medicine. 121(6 Suppl), S35-41.
- Chen, C.H., Shyu, V.B.H. and Chen, C.T. (2018). Dissolving microneedle patches for transdermal insulin delivery in diabetic mice: Potential for clinical applications. Materials, 11(9),.

- Chen, H., Zhu, H., Zheng, J., Mou, D., Wan, J., Zhang, J., Shi, T., Zhao, Y., Xu, H. and Yang, X. (2009). Iontophoresis-driven penetration of nanovesicles through microneedle-induced skin microchannels for enhancing transdermal delivery of insulin. Journal of Controlled Release, 139(1), 63–72
- Chen, J., Qiu, Y., Zhang, S., Yang, G. and Gao, Y. (2015). Controllable coating of microneedles for transdermal drug delivery. Drug development and industrial pharmacy, 3(41),.
- Chen, W., Li, H., Shi, D., Liu, Z. and Yuan, W. (2016). Microneedles As a Delivery System for Gene Therapy. Fronties in Pharmacology, 7,
- Davis, S.P., Martanto, W., Allen, M.G., Member, S. and Prausnitz, M.R. (2005). Hollow Metal Microneedles for Insulin Delivery to Diabetic Rats. IEEE Transactions on Biomedical Engineering, 52(5), 9
- Denet, A., Vanbever, R. and Gale, D.P. (2004). Skin electroporation for transdermal and topical delivery. Advanced Drug Delivery Reviews,