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REVIEW ARTICLE

Emergence of microneedles as a potential therapeutics in diabetes mellitus

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Abstract

Diabetes mellitus is a severe condition in which the pancreas produces inadequate insulin or the insulin generated is ineffective for utilisation by the body; as a result, insulin therapy is required for control blood sugar levels in patients having type 1 diabetes and is widely recommended in advanced type 2 diabetes patients with uncontrolled diabetes despite dual oral therapy, while subcutaneous insulin administration using hypodermic injection or pump-mediated infusion is the traditional route of insulin delivery and causes discomfort, needle phobia, reduced adherence, and risk of infection. Therefore, transdermal insulin delivery has been extensively explored as an appealing alternative to subcutaneous approaches for diabetes management which not only is non-invasive and easy, but also avoids first-pass metabolism and prevents gastrointestinal degradation. Microneedles have been commonly investigated in human subjects for transdermal insulin administration because they are minimally invasive and painless. The different types of microneedles developed for the transdermal delivery of anti-diabetic drugs are discussed in this review, including solid, dissolving, hydrogel, coated, and hollow microneedles. Numerous microneedle products have entered the market in recent years. But, before the microneedles can be effectively launched into the market, a significant amount of investigation is required to address the numerous challenges. In conclusion, the use of microneedles in the transdermal system is an area worth investigating because of its significant benefits over the oral route in the delivery of anti-diabetic medications and biosensing of blood sugar levels to assure improved clinical outcomes in diabetes management.

Keywords Diabetes mellitus · Insulin · Microneedles · Transdermal delivery · Biosensing

Abbreviations

Arg	Arginine
BGLs	Blood glucose levels
CMC	Carboxymethyl cellulose
CMCS	Carboxymethyl chitosan
CLA	Conjugated linoleic acid
CCA	CLA-CMCS-Arg polymer

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DM	Diabetes mellitus
EE-ASI-1	Enhanced epidermal antigen-specific immunotherapy trial-1
GUMP	Glucose measurement using microneedle patches
HbA1c	Hemoglobin A1c
HLA	Human leukocyte antigen
ISF	Interstitial fluid
LA	Lauric acid
MBGs	Mesoporous bioactive glasses
MSN	Mesoporous silica nanoparticle
MNs	Microneedles
PTMs	Phase transition microneedles
PVPMAA	Poly (vinylpyrrolidone-co-methacrylic) acid
PDA	Polydopamine
PGA	Polyglycolic acid
PLA	Polylactic acid
LGA	Polylactic-co glycolic acid
PVP	Polyvinylpyrrolidone
RS-PGC-MNs	Rapidly separating genepin-crosslinked gelatin (MNs) mounted on polyvinyl alcohol-coated polylactic acid MNs
ROS	Reactive oxygen species
SC	Subcutaneous
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
WIPO	World Intellectual Property Organization
ZnO QDs	Zinc oxide quantum dots
ZP	Zosano Pharma

Introduction

Diabetes mellitus is regarded as one of the world's most complex health issues in the twenty-first century. In reality, it has been dubbed the "Black Death of the Twenty-First Century" because of its striking resemblance to the fourteenth century Plague in aspects of prevalence morbidity, as well as mortality (Jain 2015). Diabetes mellitus affects an approximately 20.8 million people in the USA, as per the Centre for Disease Control and Prevention (Jain and Joshi 2013). In 2010, 285 million and, in 2019, 463 million adults (20–79 years) worldwide were reported to have diabetes, and these cases are anticipated to increase to 578 million by 2030 and 700 million by 2045 according to International Diabetes Federation (https://diabetesatlas.org/data/en/world/; Zhang et al. 2019a). While there are many forms of diabetes mellitus, the most common are type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes (Fonseca et al. 2020). Insulin-dependent diabetes mellitus, commonly known as T1DM, is induced by the autoimmune disruption of pancreatic beta cells, which leads to a decrease or elimination of biological insulin production (Jana and Wadhwani 2019; Galderisi and Sherr 2019). The resulting absolute insulin deficiency causes high glucose levels termed as hyperglycaemia, as well as changes in protein and lipid metabolism (Wolkowicz et al. 2021). Hyperglycaemia can cause a number of symptoms, including cardiovascular and neurological issues, whereas hypoglycaemia causes fatigue and eventually death. Although current therapeutic alternatives can regulate short-term glycaemia, none of the existing anti-diabetic medications can restore functional β-cell mass (Dong and Wu 2018; Alejandro et al. 2015). At present, the management of T2DM focuses on glucose control via lowering of fasting/postprandial blood glucose and hemoglobin A1c (HbA1c). The shortages of existing oral drugs for the treatment of diabetes include that these medications do not address the key driver of type 2 diabetes i.e., loss of functional beta-cell mass and the majority of patients do not achieve glycated haemoglobin targets (Giugliano et al. 2009; Loretelli et al. 2020). As a result, treatment failure causes a long time in controlling glycaemia, and ultimately leads to disease progression, disability, infection risks, and eventually early mortality (Gotfredsen et al. 2020). Therefore, the objective of therapy should be delay of disease progression and should specifically target the newly identified pathogenic targets of disease. Recently, sodium glucose co-transport 2 inhibitors are approved by the Food and Drug Administration (FDA) in 2013 as a new class of antidiabetic medicines but post-marketing data indicated that the use of SGLT2 inhibitor is associated with several adverse drug reactions such as diabetic ketoacidosis, cancer, bone fracture, genital and urinary tract infection, and foot and leg amputation (Singh and Kumar 2018; Singh et al. 2019). In 2014, FDA has approved dulaglutide (GLP-1 analog) for the treatment of T2DM; however, various risks associated with the use of this drug include septicaemia, malignant neoplasm, coronary artery disease, and pancreatic cancer (Garg and Kumar 2018).

Patients with insulin-dependent diabetes mellitus lose their ability to produce endogenous insulin, which can lead to blood glucose instability and ketosis without the use of exogenous insulin. The insulin-dependent diabetes mellitus treatment entails delivering exogenous insulin by injection or pump to achieve a plasma glucose level that is close to average, i.e. below 8.0 mmol/L prior to large meals for adult diabetes patients. Blood glucose levels should not drop below the normal range, i.e. 70–140 mg/dL which describes hypoglycaemia condition, leading to increased morbidity and mortality (Jana and Wadhwani 2019; Zong et al. 2021). The most common methods for treating and controlling diabetes consist of multiple regular insulin injections, as well as continuous and precise monitoring of blood glucose levels (BGLs) in order to keep their normal blood glucose levels between 70 and 140 mg/dL (Primavera et al. 2020; Liu et al.

2016; Raval et al. 2021). Because of its low oral bioavailability, insulin is normally given subcutaneously (SC); however, SC injections are linked to greater inflammation and infection danger, and also poor patient compliance. People having diabetes are frequently encouraged to subcutaneously self-administer insulin on multiple occasions per day; this necessitates both intensive self-management and training, including regular dose modifications by patients depending on glucose monitoring. Furthermore, repeated injections in the same place can cause thickening of skin and inadequate glycaemia regulation, leading to poor diabetes management. Several other new and minimally invasive delivery mechanisms, like buccal, oral, transdermal, and nasal systems, are being studied to ascertain their efficacy and improved patient compliance in order to mitigate these limitations; however, such technologies are mostly still in preclinical development (Fonseca et al. 2020; Ross and Neville 2019; Tucak et al. 2020).

One of the most notable aspects of current efforts of researchers is the invention of the microneedle (MN) patch, which can successfully overcome the implicit barriers to insulin absorption through the skin and therefore facilitate transdermal drug delivery despite the use of complex systems or external energy sources (Chen et al. 2020a; Hultström et al. 2014; Thuillier et al. 2018). Without causing pain, the micro-scaled needles can penetrate the outermost keratinous stratum corneum layer and enter the epidermal and dermal layers of the skin for drug release (Alimardani et al. 2021; Dharadhar et al. 2019). MN creates temporary micro-channels for drug transport, but they immediately heal after MN is removed, preventing long-term skin tissue injury (Jin et al. 2018).

Diabetes is one of the most prevailing health issues in recent times due to highly busy scheduled lifestyle of the modern era people, as the people are not having enough time to go for the exercises to burn their calories and use their body glucose as a source of energy which leads to the accumulation of glucose in the muscles and blood and increases the glucose levels in the blood above the normal range, giving rise to diabetes, which leads to serious health problems. Therefore, this needs immediate care as well as treatment. In this review, we give an overview of several types of diabetes with an emphasis on pathophysiology and causes. This article discusses the several types of MNs available and their drug release patterns in the skin after insertion, as well as glucose monitoring in diabetic patients using blood or interstitial fluid samples. This review describes the various potential and applications of the MNs and also includes a brief summary of recent patents and the current clinical status of MN use in diabetes. The primary search engines employed throughout the paper search strategy were PubMed, Google Scholar, ScienceDirect databases, and Web of Science. Literature review was done using publications published in peer-reviewed journals from the year 2004 to year 2021.

Pathophysiology of diabetes mellitus

Type 1 diabetes mellitus

T1DM is now widely accepted as an autoimmune disease caused by the destruction of insulin-producing pancreatic cells (Zaccardi et al. 2016). As a result of this process, insulin deficiency develops, eventually leading to full dependence on exogenous insulin (Brinkman 2017). Beta cells regulate and generate insulin as well as acting as glucose sensors (Bluestone et al. 2010). As the number of beta cells in the body decreases, less insulin is produced to maintain blood glucose homeostasis, leading to a rise in blood glucose levels (Cnop et al. 2005). The individual with diabetes can no longer control their blood glucose levels due to the loss of beta cell mass. If left untreated, this can cause a person to become sick in a short period of time, with the risk of developing diabetic ketoacidosis (Devendra et al. 2004). Further consequences on this condition could end up with diabetic coma as sequentially represented in Fig. 1.

Type 2 diabetes mellitus

The steady decline in ß-cell function that occurs against a background of insulin resistance leads to changes in glucose metabolism. Insulin secretion and insulin sensitivity are the two most important aspects of the blood glucose control mechanism (D'Adamo and Caprio 2011). Insulin resistance is a defining characteristic of T2DM, and it affects more than 90% of patients (Imam 2013). A reduction in the metabolic response of insulin-responsive cells to insulin or, at a systemic level, an inadequate/decreased response to circulating insulin by blood glucose levels is referred to as insulin resistance (Galicia-Garcia et al. 2020). The liver and muscles have long been known to have a role in systemic insulin resistance. During fasting, the liver generates glucose from non-glucose substrates via gluconeogenesis process to assure that a carbohydrate energy source is always available. Several investigations have found that people with T2DM have enhanced gluconeogenesis despite having hyperinsulinemia, implying that hepatic insulin resistance is a major factor in fasting hyperglycaemia. The causes of decreased hepatic insulin sensitivity are unknown; however, a deposition of fat in the liver (steatosis) is thought to be a major factor (Koufakis et al. 2021; Zaccardi et al. 2016). The second and as important pathogenic factor is a reduction in β-cell dysfunction. Insulin is generally released in two stages in response to increased glucose levels: first, a rapid first-phase release (0–10 min), then by a longer second phase (10–120 min),

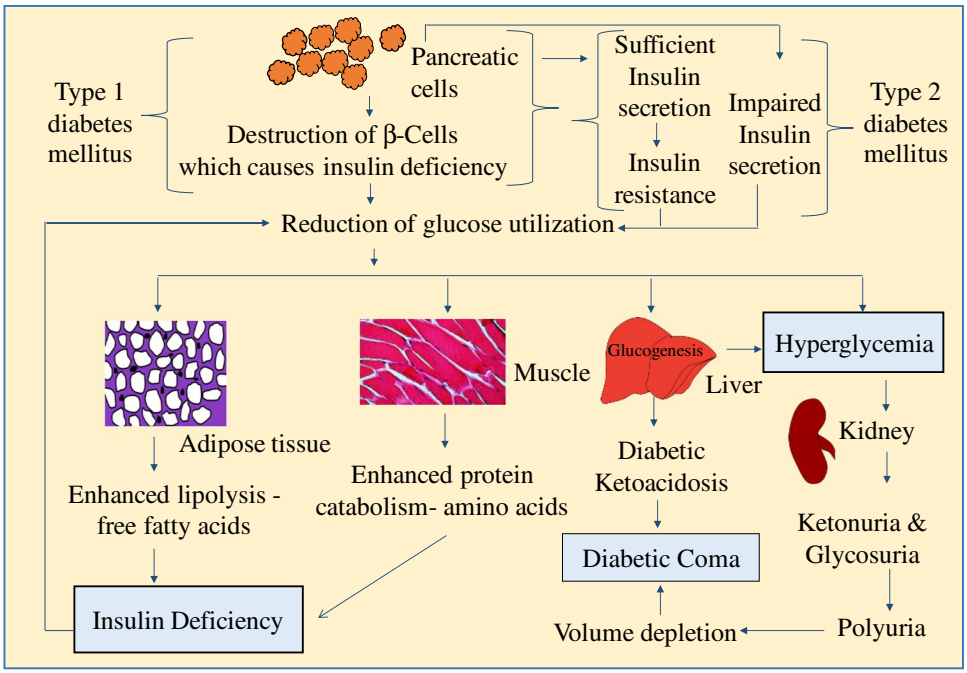

Fig. 1 Pathophysiology of type 1 and type 2 diabetes mellitus which leads to reduction of glucose utilization by adipose tissues, muscles, and induction of glucogenesis by liver ultimately causing hyperglycaemia and diabetic coma

which lasts as long as essential to sustain euglycaemia. First-phase insulin production is lost after fasting glucose levels reach 115–120 mg/dL. The β-cell function has already been lowered by 60–70% by the moment poor glucose tolerance develops with glucose levels of 141–199 mg/dL 12 h after the challenge (Imam 2013). Insulin secretory failure, the fundamental cause of β-cell dysfunction and the base of T2DM, can be caused by deficiencies in the production of insulin intermediates or insulin itself, and also a disruption in the secretion process (Hoang Do and Thorn 2015). The sequential illustration of pathophysiology of T1DM and T2DM is described in Fig. 1.

Assessment of diabetes risk factors for type 1 diabetes mellitus

Genetic and environmental factors

Genetic mutations account for about one-third of disease sensitivity while environmental factors account for the other two-thirds. About 40% of the genetic risk is attributed to genes connected to the human leukocyte antigen (HLA) locus. HLA-DR3 or HLA-DR4 is found in around 95% of T1DM patients. The other significant gene, located in the 5' polymorphic region of the insulin gene, provides nearly 10% of the genetic risk (Imam 2013; Kerner and Brückel 2014). HLA genes, which encode cell surface proteins implicated in antigen presentation and self-tolerance, are crucial in controlling the immune response. As a result, genetically controlled changes in the amino acid sequence of these proteins can modify the repertoire of peptides given, leading to the loss of self-tolerance. These findings, together with current understanding of a link between HLA and other autoimmune disorders, as well as evidence of the efficacy of immunosuppressive medications on T1DM disease progression, greatly supported the notion that "insulin-dependent" diabetes was an immune-mediated disease implicating the pancreatic islets of Langerhans (Zaccardi et al. 2016; Von Herrath et al. 2016). Vitamin D deficiency has long been believed to be a risk factor for developing T1DM. Consumption of meat preservatives and alcohol are some other factors that may contribute to the development of type 1 diabetes (Mayo 2016).

Co-existent autoimmunity

Immune-mediated diseases such as thyroid disease and celiac disease have been related to T1DM. However, it is unknown whether they constitute risk factors for the disease. Thyroid auto-antibodies are found in about 25% of children with T1DM when they are diagnosed, and thyroid dysfunction is more common in people with T1DM than in those without the disease. T1DM patients are more likely to develop celiac disease than non-diabetic patients. Thyroid disease and celiac disease affect metabolic regulation; if left untreated, they can increase the risk of hypoglycaemia in people with T1DM (Chiang et al. 2014, 2018). Once a person is diagnosed with T1DM, the only way that allows them to live is to replace the missing endogenous insulin by

subcutaneous insulin injections at periodic intervals every day for the rest of their lives (Bluestone et al. 2010).

Assessment of diabetes risk factors for type 2 diabetes mellitus

Multiple factors, like β-cell mass and secretory capacity, which are affected by genetic and environmental variables, influence the ability of the β-cell to release adequate insulin to effectively respond to the peripheral insulin resistance condition. In fact, various metabolic derangements (insulin resistance, lipotoxicity) could cause progressive loss of β-cell function.

Reduction in β-cell mass

The reduced β-cell mass may play a role in explaining lower maximal secretory capability for insulin secretion in people with T2DM. This decrease in mass, however, cannot account for the complete pattern of functional alterations seen in T2DM. As a result of the altered metabolic state, like elevated glucose and free fatty acids, as well as amyloid deposits, a rise in programmed cell death, also called apoptosis, may occur (Pozzilli et al. 2011; Weir et al. 2020).

Nutritional factors

The high-calorie Western diet comprises considerable quantities of carbohydrates and fats, which raise glucose levels of blood and circulating triglyceride-rich chylomicrons, and very-low-density lipoproteins. This causes an increase in the levels of reactive oxygen species (ROS), which results in aberrant inflammatory molecule production. Since oxidative stress is a renowned inducer of inflammation, the two processes interact synergistically after a large meal, increasing the negative postprandial consequences. The pathogenesis of T2DM is aided greatly by a prolonged and considerable rise in steady-state ROS levels (DeFronzo et al. 2015).

Western lifestyle

A Western lifestyle is typically connected with high-energy foods and less physical activity. The broad availability and intake of high-fat, high-sugar, energy-dense processed convenience meals add considerably to the obesity epidemic that has gripped developed countries. Also, these diets are often lacking in vitamin D, vitamin B_{12}, and folic acid, all of which have been associated to the development of T2DM (Nolan et al. 2011; Kahn et al. 2014).

Endocrine-disrupting chemicals

Chemicals that affect the endocrine system function and induce severe health effects like T2DM have been identified. Pesticides, cosmetic preservatives and food, components and compounds used in the plastics sector, consumer products, and waste incineration by-products are all examples of endocrine-disrupting chemicals. These chemicals are all around us, and they are impossible to avoid (Chevalier and Fénichel 2015).

Microneedle technology

The use of MN technology for drug delivery via and into the skin and other target tissues has advanced significantly over the last decade (Sharma et al. 2019; Mdanda et al. 2021). MNs were first suggested as a drug delivery tool in the 1970s, and since then, they have been produced using a range of technologies, materials, and geometries (He et al. 2019). MNs have been thoroughly researched in the production of insulin patches (Ng and Gupta 2020). Microneedles are classified as solid or hollow cannulas with an external diameter of less than 300 mm and a length of 50–900 mm (Queiroz et al. 2020). The MN system is focused on the painless piercing of the skin by several needles inside a patch that are micrometres in size (less than 1 mm in length) to administer insulin in a minimally invasive and targeted manner (Chen et al. 2020a). Whenever the patch is applied to the skin whether manually or by an applicator, MNs with lengths varying between 100 to 1500 μm puncture the outermost layer stratum corneum having a width of 10–20 μm and penetrate via the skin epidermis to a level of 70 to 200 μm. Microchannels produced in this way serve as temporary hydrophilic pathways in the skin, allowing small drugs like alendronate, macromolecules, and nanoparticles to be transmitted to the skin. The dermis's dense capillary bed allows the medication to be absorbed quickly. Skin integrity is restored, as determined by transepidermal water loss, and microchannels reclose within hours (El-Khordagui 2012).

Silicon, glass, metal, polymers, and less conventional materials such as carbohydrates have all been used to make MNs. The large numbers of silicon-based MNs for clinical use are engraved perpendicular to the silicon wafer surface and are called "out-of-plane" designs (Yang et al. 2020). Strong and hollow MNs are the two broad types of MNs. Non-dissolving and dissolving/degradable MNs are also solid MNs. Drugs can be administered through MN-treated skin in a number of ways, including (a) "poke and patch", which involves skin pre-treatment using solid MNs accompanied by topical application of drug preparation or patch on microporated skin; (b) "coat and poke", which involves coating solid MNs with the drug and inserting them into the

skin, allowing accurate dosing and skin administration of unstable drugs; (c) "poke and release" using drug-loaded solid MNs composed of dissolving/biodegradable polymers or polysaccharides enables concurrent skin microporation and drug release in one step. There is no need for a patch or a micropump, and there is no dangerous sharp waste left; (d) "poke and flow", which involves injecting a liquid drug preparation into the skin using hollow MNs. Hollow MNs may also be utilized to take a sample of dermal interstitial fluid for glucose testing (El-Khordagui 2012).

Microneedles as an emerging therapy for diabetes mellitus

Diabetes mellitus (DM) has been a global health problem for many decades and is now the fifth leading cause of death. DM is a metabolic disorder with several aetiologies that affects several organs and contributes to a number of cardio-vascular and neuropathic complications. In clinical terms, DM is defined as an increase in blood glucose levels and a decrease in plasma insulin levels (Zaric et al. 2019). Type 1 and type 2 diabetes mellitus are the two main types of diabetes mellitus (T1DM and T2DM). T1DM is caused by an absolute lack of insulin, while T2DM is caused by a combination of insulin resistance, impaired insulin secretion, and increased glucose production. T1DM is divided into two types, i.e. type 1A (autoimmune destruction of ß-cells) and type 1B (idiopathic insulin deficiency) (Mohsen 2019). The new normal treatment for type 1 diabetics with inadequate insulin secretion is to keep BGLs under tight control via regular exogenous insulin subcutaneous injection. Type 2 diabetes is characterised by insulin resistance that can be controlled by exercise, a healthy diet, or oral anti-diabetic medicines. Insulin administration is also necessary to effectively control BGLs in people with advanced type 2 diabetes. In order to achieve effective glucose regulation, many insulin formulations are currently available on the market. Owing to the increasing degradation of insulin in the gastrointestinal tract, numerous routes of insulin administration have been studied, including subcutaneous injection, nasal, pulmonary, and transdermal delivery. Because of their high absorption capacity and distribution performance, subcutaneous insulin administration through hypodermic injection or pump infusion is still the preferred method, but SC injections are linked to higher inflammation and infection risk, as well as poor patient compliance. Minimally intrusive alternative routes such as oral, pulmonary, nasal, buccal, peritoneal, and transdermal administration have been studied to address these disadvantages. Transdermal insulin administration, in particular, has gained popularity in recent decades due to its ease of use and increased patient adherence. MNs have recently gained popularity as a convenient and minimally invasive way to self-administer this medication. Since the stratum papillare of the skin is rich in small vessels, MNs have the potential to speed up insulin absorption (Chen et al. 2020b; Vora et al. 2020; Wang et al. 2020a). MN system is produced by arranging hundreds of MNs in arrays on a tiny patch (similar to a commercially available transdermal patch) to deliver enough medication to produce the desired therapeutic response (Waghule et al. 2019; Jung and Jin 2021). For drug release, the micro-scaled needles will penetrate the stratum corneum and enter the epidermal and dermal layers without causing pain. MN creates temporary micro-channels for drug delivery, but they rapidly heal after MN is removed, preventing long-term skin tissue damage (Zhang et al. 2019b). The dermis has a lot of blood capillaries and is relatively hydrophilic. Insulin can swiftly circulate throughout the dermis and then be absorbed into systemic circulation through blood capillaries, resulting in a therapeutic reaction when it reaches the site of action (Shen et al. 2020; Bilal et al. 2021). MNs have a base width or diameter of around 200 to 300 µm, which is substantially greater than the diameter of a follicle of approximately 100 µm. As a result, MNs aid macromolecule dispersion through the skin by forming drug-permeating channels. MN tips may penetrate the nerve-distributed skin layer; their scale is so minute that they cause minimal damage or activation to nerves (Wang et al. 2020b).

Types of microneedles

Solid microneedles

Metals, silicon, and polymers, such as polycarbonate, have all been used to make solid MNs. The first solid MNs were fabricated from silicon using microfabrication technology (Puri et al. 2021). Solid silicon MNs emerged as the most common method due to their high biocompatibility (Agrawal et al. 2020). Solid MNs are stronger and have a better mechanical strength than hollow MNs (Yadav et al. 2020). MN-assisted transdermal administration using solid MN is also referred to as the "poke with patch" method as depicted in Fig. 2 (Xie et al. 2015). Solid MNs may be used as a skin pre-treatment to create large pores for drug delivery. Topical formulations like lotion, gel, and ointment required to cure skin can be delivered into the dermis via the pores once they have created. They can then be dispersed across the body via systemic circulation (Duarah et al. 2019).

Coated microneedles

The use of coated MNs in transdermal delivery of MNs is an appealing process (Xie et al. 2015). Coated MNs may be made of silicon or metal, and the medicine is packed

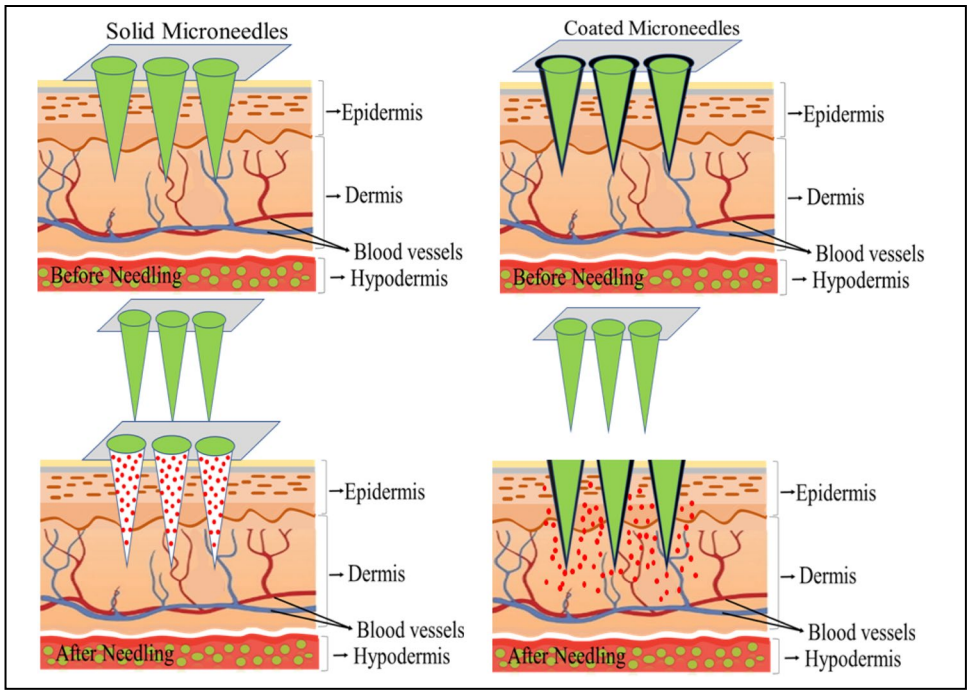

Fig. 2 Pictorial representation of solid microneedles (left side) and coated microneedles (right side) showing intra-dermal drug delivery to blood vessels via skin needling (before and after) procedure

onto the individual needles of the MN array as a coating layer in a dry state (Tarbox et al. 2018). The drug delivery pattern from coated MNs via skin layers is depicted in Fig. 2. Coated MNs serve two functions; the first is to penetrate the skin, and the second is to add required drugs to the surface of the MNs. Regrettably, the maximum drug dosage is less than 1 mg; therefore, the production of coated MNs is limited (Ingrole and Gill 2019).

Hollow microneedle patch

Microelectromechanical system techniques have been used to create hollow MNs in a variety of heights and shapes, primarily out of silicon and metal. MNs made of polymeric materials, hollow glass, and ceramics have also been produced (Cárcamo-Martínez et al. 2021). Hollow MNPs are made up of hollow needles that allow for continuous

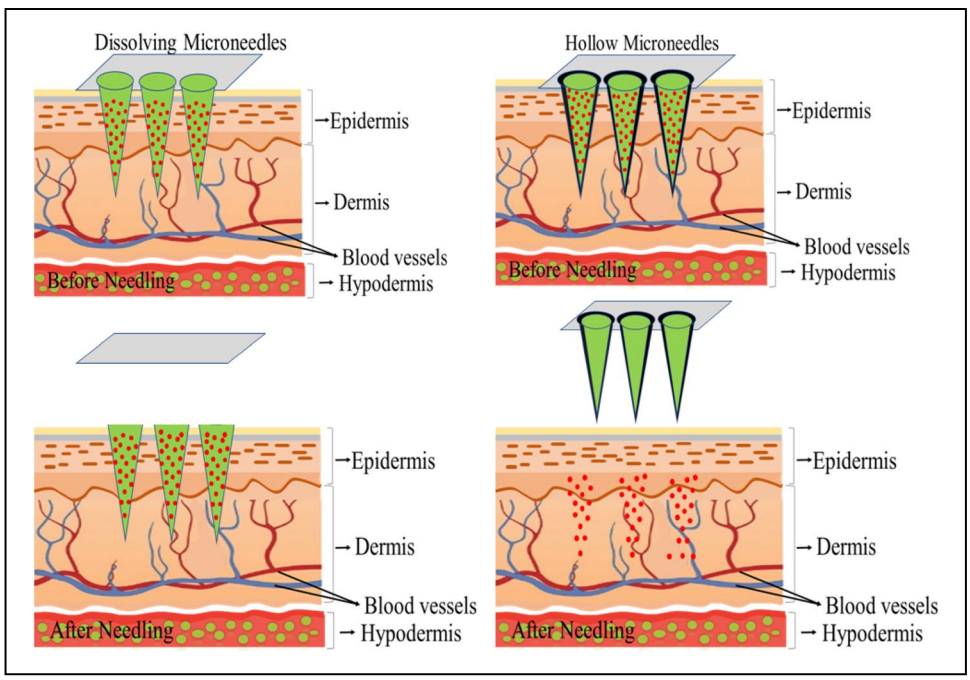

Fig. 3 Diagrammatic illustration of dissolving microneedles (left side) and hollow microneedles (right side) revealing intra-dermal drug delivery via skin needling procedure for direct drug delivery in blood vessels with minimum invasion

insulin delivery into the skin (Tarbox et al. 2018). After the needle is injected into the tissue, the medicine is permitted to pass via the hole and then into the systemic circulation (Fig. 3). Some of the benefits of this form of transdermal delivery include drug distribution rates can be controlled with a pump; drug administration amounts are far greater; and accurate dosage led to very effective delivery (Xie et al. 2015).

Dissolving microneedles

Insulin is encapsulated in the polymeric matrices of a dissolving/degradable MN patch composed of soluble/degradable polymer materials. Insulin is released when a polymer dissolves or degrades, and the rate at which insulin is released is regulated by the rate at which matrices dissolve or degrade (Wang et al. 2020c). Since the MN is not withdrawn after injection like in other situations, there is only one step to the procedure (Fig. 3). Within the skin, the polymer degrades and regulates drug release. The bioacceptability of the polymer and its breakdown within the skin make it one of the best options for long-term therapy with better patient compliance. When designing dissolving microneedles, efficient needle drug delivery is a critical component that confronts challenges. As a result, mixing of polymer and the drug is an essential stage in the manufacturing process (Waghule et al. 2019). Numerous dissolving MNs composed of sugar glass polymers, like maltose and trehalose, have been identified to date. After insertion, sugar glass MNs typically dissolve rapidly in human skin. The production of these MNs, however, necessitates an elevated temperature of over 100 °C to cause rubber to glass transitions of sugar glasses, which can impair the bioactivity of biomolecules such as insulin (Jeong et al. 2021).

Hydrogel-forming or phase transition microneedles (PTMs)

Microneedles that form hydrogels are made of cross-linked hydrophilic polymers. Phase transition microneedles (PTMs) are strong enough in their dry glassy condition to pierce the epidermis and transform to a water-swollen hydrogel via absorbing interstitial fluid in the dermis layer. The preloaded insulin in the MNs diffuses quickly into the skin via hydrogel network. The cross-linking between the molecular chains allows the PTMs to retain their hardness when hydrated, ensuring that they are completely removed from the skin following application (Shen et al. 2020). In a nutshell, Table 1 summarizes differentiating features between various types of earlier explained microneedles (Fig. 4).

Application of microneedles in glucose monitoring

The diagnosis of all forms of diabetes, at an early stage, is important for the management of the disease to slow down potential complications such as retinopathy, diabetic nephropathy, cardiovascular diseases, neuropathy, diabetic foot ulcer, and viral infections (Szunerits et al. 2021; Baghban et al. 2019). The advantages of strict glycaemic regulation towards the management of blood glucose levels in diabetic patients have long been known. Continuous glucose monitoring can significantly minimize the incidence of diabetes-related diseases, allowing diabetics to maintain a healthier lifestyle while avoiding expensive and life-threatening late-stage diabetic complications (Teymourian et al. 2020; Juska and Pemble 2020). Microneedles can be explored as a glucose-sensing component in glucose monitoring. Glucose sensing may be performed with blood or interstitial fluid (ISF) samples. The biofluid to be sampled is the most important factor in MN design. Several studies have been carried out on the relationship between blood glucose levels in blood and ISF. It has been widely reported that there exists a time lag in the distribution of glucose from blood to ISF. The lag time is estimated to be between 0 and 45 min (Mathur et al. 2010). Blood and ISF glucose levels, on the other hand, are strongly correlated once equilibrium is achieved. It essential to understand the physiological dissimilarities between blood and ISF in order to better understand design differences between blood and ISF extracting microneedles (Khanna et al. 2008; Bariya et al. 2012).

Microneedles for interstitial fluid (ISF) sampling

For a variety of analytes, MN-mediated sampling of interstitial fluid is evolving as a promising alternative to blood sampling, with glucose being a major target. Because of their short length (less than 1000 m), MNs can penetrate the stratum corneum and enter the ISF in the viable epidermis and top layers of the dermis without stimulating nociceptors or touching blood vessels, making them a minimally invasive method of extraction (Wang et al. 2019; Kap et al. 2021; Jendrike et al. 2017). Fracture and buckling are two possible failure scenarios of MNs. Shorter needles with the same diameter and material can generally tolerate greater pressure without breaking. As a result, needles made of lower-strength materials, such as silicon dioxide, can be utilized for ISF sampling. Another benefit of silicon dioxide is that it is highly biocompatible. Because of the lower height, smaller needle diameters may be used without causing buckling (Friedl 2005; Sivamani

Table 1 Tabular representation of distinctive parameters differentiating amongst various types of microneedles

Parameter	Solid microneedles	Coated microneedle	Hollow microneedle patch	Dissolving microneedles	Phase transition microneedles
Application	Used for skin pretreatment	Used to enhance the transdermal permeation ability of drugs	Used for high molecular weight compounds such as proteins, vaccines, and oligonucleotide	Used as a skin pretreatment to increase permeability	Used to enhance the effectiveness of transdermal drug delivery
Permeability	Increase the permeability by pocking the holes in skin, rub drug over or coat needle with drug	Mechanism of drug delivery is coat and poke approach	Deposits drug directly into the epidermis or the upper dermis layer upon inserting into the skin as they possess holes at the tips	Mechanism of drug delivery is poke and release approach	Swell when inserted into the skin, leads to the formation of channels between the capillary circulation and the drug patch and behave as a rate-controlling membrane
Mechanism of drug penetration	Penetrate into the dermis, forms micron-sized channels, and then drug enters via these channels (passive diffusion) and channels close as soon as needles are removed so toxic substances or infection can be prevented	Drug coated on microneedle tips released into skin on insertion into the skin	Drugs delivered into the skin directly through the holes present at the tips in hollow microneedles	After inserting, polymer gets degraded inside the skin and releases the encapsulated drug	On insertion, uptake water and swell which makes them suitable for biomedical applications
Size	Fabricated in 750–1000 µm in length	600–900 µm in height	5–70 µm width and height 250 µm	Length less than 1000 µm	Length of needle (500–800 µm), diameter of needle base (150–300 µm), tip diameter (< 15 µm)
Drug delivery approach	Poke and patch	Coat and poke	Poke and flow	Poke and release	-
Materials used for fabrication	Metals, polymers, and silicon	Silicon or metal	Silicon, metal, hollow glass, polymeric and ceramic	Biocompatible and biodegradable polymers, i.e. PLA, PGA, PVP, PVP-MAA, sodium hyaluronate, chondroitin, carboxymethyl cellulose, and amylopectin	Aqueous blends of polymeric materials (i.e. poly (methyl vinylether/ maleic acid) and poly(ethylene glycol)

PLA, polylactic acid; *PGA*, polyglycolic acid; *PLGA*, polylactic-co glycolic acid; *PVP*, polyvinylpyrrolidone; *PVPMAA*, poly (vinylpyrrolidone-co-methacrylic) acid.

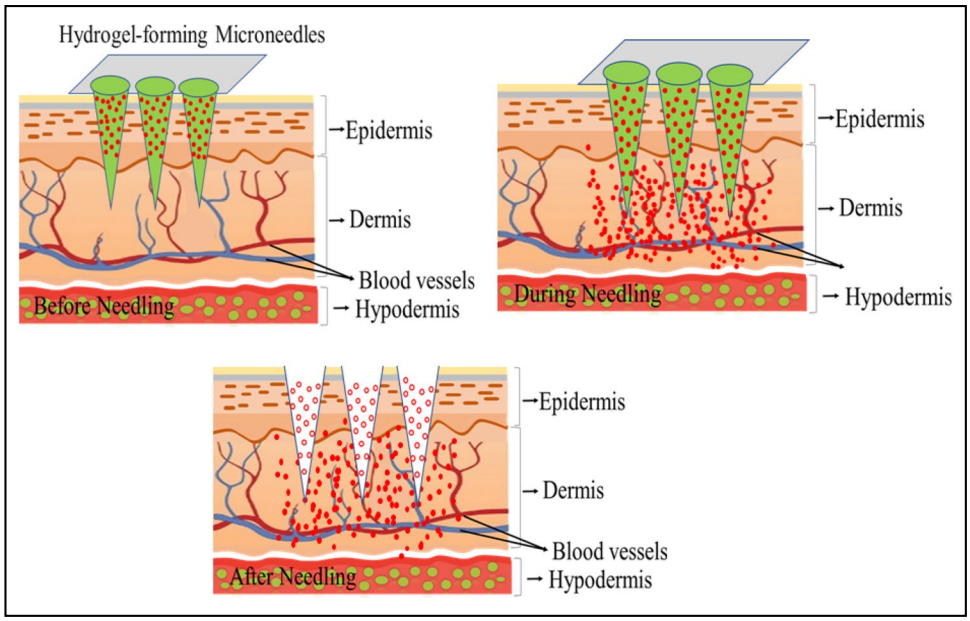

Fig. 4 Diagrammatic illustration of hydrogel formation of hydrogel forming microneedles during skin needling procedure for intra-dermal drug delivery in blood vessels

et al. 2009; Davis et al. 2004). With a narrower tip diameter, the ratio of fracture force to insertion force into skin is much greater (Ranamukhaarachchi et al. 2019). This improves the safety margin for using MNs without failure. For ISF sampling, MN lumen diameters can be as small as 10 µm in most cases. Extremely high capillary forces are produced by a small MN diameter combined with a low density of ISF. Capillary forces significantly increase as the hydrophilicity of the MN material raises. And without a pumping system, this makes fluid extraction easier. Unfortunately, as the diameter of the MNs decreases, the flow rate also decreases. As a result, before the MNs are loaded with ISF, there is an initial latent time. The majority of commercial ISF glucose sensors only need 0.5–2 µl of fluid, and this figure is steadily decreasing. An array of MNs is employed to accomplish the necessary flow rates in order to improve flow rates. In humans, vacuum pump-assisted ISF sampling with MNs has been established and proved to monitor changing glucose levels with a time lag of less than 20 min following insulin injection (Kolluru et al. 2019; Jiang and Lillehoj 2020; Samant and Prausnitz 2018; Miller et al. 2018).

Microneedles for blood sampling

Blood capillaries are found deep under the epidermis. Commonly, blood microcapillaries are located at 400-µm penetration depths. In the same depth, the nerve tips can also be found. As a result, some of the MNs in the array can only scratch the nerve cells at the top. The narrow diameters and regulated shank length, on the other hand, minimise the chances of encountering a nerve or stimulating it sufficiently to cause significant pain. In a study of the impact of MN design on pain in humans, researchers discovered that needles varying in length ranging from 480 to 1450 µm resulted in pain scores of 5 to 40% of a 26-gauge hypodermic needle. MN shank lengths of 400–900 µm are required to extract blood without causing severe pain. The MNs must be made of stronger materials like metal or silicon at these lengths. The size of a female mosquito proboscis is a popular model used by researchers (Li et al. 2013). The diameter of the MNs must be large enough to allow easy access to the largest blood cells. Also, the longer length requires greater diameters to avoid needle failure via buckling. Typical MNs diameters must be at least 50 µm in width. And although capillary action alone can be sufficient for blood extraction, factors like greater fluid density, greater conduit diameter, and material of choice can all help to minimize the impact. In these circumstances, a microfluidic pumping device is required to produce negative pressure (Lisi et al. 2020; Zhang et al. 2019c).

Recent advancements in microneedle-based treatment modalities for management of diabetes mellitus

The MN technique is being used for various medicines, but it must overcome a number of obstacles before being commercially available. It will take a lot of research to get it clinically authorized. Skin allergies, redness, and irritation are the most common concerns connected with MN technology. The MNs can only hold a small quantity of medicines. It is extremely difficult to pass hydrophilic and big substances through the skin. In order to fabricate these needles, the ideal material must be used that has sufficient mechanical

toughness and insertion force. The basic goal is to enhance permeability without creating discomfort. A patient may find it extremely challenging to poke with a needle and then put the patch. If the skin pores do not seal following application, there is a risk of infection (Ita 2015). In spite of these challenges, the MN-based method appears to be the most widely studied field, serving as a foundation for drug penetration and dermal delivery. Most studies have revealed that it can provide sustained release of drugs over a long period of time while avoiding a rapid drop in blood glucose in the early phase to avoid hypoglycaemic side effects. However, we are unable to manage drug release depending on variable glucose levels using simply MN administration without additional features like biosensors which would be beneficial in this regard, as the release of drug would be triggered by the glucose level. One of the challenging issues encountered while using MNs is achieving precision of measurement and correlation between results acquired from interstitial fluid or sweat and plasma or blood glucose (Tarbox et al. 2018; Sharma et al. 2019; Puri et al. 2021). Table 2 summarizes the various recent advancements in MN-based treatment modalities for management of diabetes mellitus.

Patent literature focussing application of microneedles in treatment of diabetes mellitus

Patent literature searches were performed from the official website of World Intellectual Property Organization (WIPO) with analytics to ensure and categorize the current research about the applications of MNs in diabetes mellitus from the period of 2014 to date (Table 3). The keywords entered in search strategy were “insulin”, “microneedle”, “diabetes mellitus”, “therapy”, and “delivery”, “in various combinations”. This literature would increase understanding and prospective for research scientists to comprehend better outlook in the research and development of MNs systems for treatment and monitoring of diabetes.

Current clinical status spotlighting expedient role of microneedles in diabetes mellitus

Various pre-clinical studies on MNs have been conducted and proved to be beneficial in several areas, but only a few have undergone success in human patients (https://clinicaltrials.gov/). Numerous clinical trials based on applications of MNs for monitoring and treatments of diabetes conditions are currently under different phases carried by several universities and industries (Table 4).

Conclusions

MNs are emerging as essential physical enhancers in transdermal drug delivery and fluid extraction systems, and their importance will grow as a result of the benefits they provide and it has the potential to replace traditional drug delivery approaches, most notably the transdermal approach. MN devices have shown tremendous promise in enhancing insulin penetration by breaking the skin barrier, as contrasted to passive transport via the skin. Unlike traditional hypodermic injections, insulin delivery through MNs has the advantages of requiring little training and painless insertion. However, MN-based delivery has a number of drawbacks, such as less accurate dosage accuracy than hypodermic needles, variances in skin layer thickness and skin hydration among individuals, drug delivery issues related with non-vertical insertion of the MNs to the skin, harm to veins with repeated use, and probable breaking of the MNs tip or the entire MNs within the skin. A greater understanding of the pharmacokinetics of insulin delivered intradermally using MNs may also be beneficial. Furthermore, the effectiveness of increasing skin penetration, which is one of the most significant challenges in transdermal drug delivery, has expanded the reach of MN drug delivery in the coming years.

Current status and future prospects

Silicon was used to create the first MNs and an analysis was carried to see if MNs might be utilized to more effectively administer medications via the skin. First, permeation studies on cadaver skin were conducted to investigate if big molecules such as albumin and insulin could pass via the skin when MNs were used. Microneedles were found to deliver big molecules more effectively in subsequent investigations. Many new fascinating MN concepts are now being developed that will be extremely beneficial in the future (Christensen and Gannon 2019; Gastaldelli 2011; Marselli et al. 2014). MNs, as a new device, have distinct benefits (painless and quick delivery) over previous systemic administration methods, and they offer a variety of biomedical applications (Rao et al. 2014). The MN-based method appears to be the most widely studied field, serving as a foundation for drug penetration and dermal delivery. Most studies have revealed that it can provide sustained release of drugs over a long period of time while avoiding a rapid drop in blood glucose in the early phase to avoid hypoglycaemic side effects (Rojas et al. 2018).

In microneedle research, there is more than enough space for advancement. For example, novel materials for

Table 2 Microneedle-based treatment modalities for management of diabetes mellitus

Drug	Excipients	Dosage form	Outcome and significance	Reference
Insulin	Polydimethylsiloxane, gelatin, fluorescein 5(6)-isothiocyanate, sodium carboxymethyl cellulose (CMC)	Two-layer dissolving polymeric MN patches	Use of gelatin/CMC MN patches for insulin delivery resulted in a satisfactory relative bioavailability, making it an attractive device for delivering low permeable protein preparations for diabetic therapy	(Lee et al. 2017a)
Insulin	Polydimethylsiloxane, gelatin, fluorescein 5(6)-isothiocyanate, rhodamine 6G, sodium carboxymethyl cellulose	Dissolving MN patches	A simple two-layer gelatin/CMC MN patch was an excellent alternative to traditional insulin injection, and dissolving gelatin/CMC MNs were potentially useful devices for transdermal delivery of various biomolecules	(Chen et al. 2018a)
Insulin	Gelatin, fluorescein, 5(6)-isothiocyanate, citric acid, streptozotocin, fluorescein isothiocyanate-dextran, insulin, polydimethylsiloxane	Dissolving polymer MN patches	Starch/gelatin MNs allow quick and reliable delivery of insulin into the skin in diabetes treatment and were potential devices that might provide a convenient self-administration alternative for the transdermal delivery of diverse biomolecules	(Ling and Chen 2013)
Proinsulin	Polysorbate 80, aliquot of proinsulin powder	PI-coated MNs	Proinsulin could be uniformly and reproducibly coated on solid MNs to produce a delivery system that could deliver therapeutically relevant dose of PI into the skin to stimulate a local immune response	(Arikat et al. 2020)
Insulin	Acrylamide, acrylic acid, human regular insulin, azobisisobutyronitrile, fluorescein iso-thiocyanate labelled insulin, N,N'- methylbisacrylamide	Lyophilized hydrogel patches	Provided a convenient and effective administration strategy for MN-mediated insulin delivery and, also provided a promising foundation for MN-mediated delivery of other macromolecules such as proteins and peptides	(Qiu et al. 2012)
Insulin	Polyvinylpyrrolidone (PVP), anhydrous sodium carbonate, sodium citrate tribasic dihydrate, dimethyl sulfoxide, insulin, streptozotocin, fluorescein isothiocyanate, 3-(4, 5-dimethyl-thiazol-2-yl)-2,5-diphenyl tetrazolium bromide	Insulin-loaded calcium carbonate/PVP MNs	In comparison to pure PVP MNs, and conventional subcutaneous injection technique, the insulin-calcium carbonate/PVP MNs presented a good potential device to deliver insulin for diabetic therapy	(Liu et al. 2018a)
Metformin	Sulfur, copper (II) nitrate trihydrate ($Cu(NO_3)_2.3H_2O$, oleylamine, 1-octadecene, streptozotocin, lauric acid, polycaprolactone, polyvinyl alcohol, polyvinylpyrrolidone	NIR-induced photo-triggerable MNs	Implantable MNs showed efficient hypoglycaemic behaviour in diabetic rats	(Zhang et al. 2018a)
Insulin	Sodium alginate, fluorescein isothiocyanate isomer I, streptozotocin, calcium chloride anhydrous, Polydimethylsiloxane, citric acid, D- (+)-maltose monohydrate, sodium citrate tribasic dihydrate	Ca^{2+}/alginate-maltose MNs	Ca^{2+}/alginate-maltose MNs presented a promising device for diabetic therapy via transdermal ingestion	(Zhang et al. 2018b)
Metformin	Poly(vinylpyrrolidone), Polydopamine (PDA), lauric acid (LA), tetraethyl orthosilicate, anhydrous sodium carbonate, cetyltri-methyl ammonium bromide, methyl thiazolyl tetrazolium, streptozotocin, polydimethylsiloxane	Drug-loaded and PDA/LA-coated hollow mesoporous silicon dioxide nanoparticle	In diabetic models, the near-infrared-triggered MNs transdermal delivery system showed better drug release actions as well as effective hypoglycaemic activity in a reasonably convenient and initiative manner	(Zhang et al. 2018c)

Table 2 (continued)

Drug	Excipients	Dosage form	Outcome and significance	Reference
Metformin	Poly(vinylpyrrolidone), anhydrous calcium chloride, bismuth nitrate pentahydrate, anhydrous sodium carbonate, lauric acid, sodium borohydride, dimethyl sulfoxide, citric acid, streptozotocin	Bismuth nanodots	Coated and dissolving MNs with near-infrared-triggered medication release offered an effective alternative to conventional subcutaneous injection, enabling both fast and effective hypoglycaemia control	(Liu et al. 2018b)
Insulin	Calcium sulfate hemihydrate, gelatin, rhodamine B, glutaraldehyde solution, fluorescein isothiocyanate isomer I, polydimethylsiloxane, sodium citrate tribasic dihydrate	Biodegradable composite MN patches	Biodegradable composite MNs containing insulin have a potential application in diabetes treatment via transdermal ingestion	(Yu et al. 2017a)
Insulin	Calcium nitrate tetrahydrate [Ca $(NO_3)_2 \cdot 4H_2O$], ammonium dihydrogen phosphate $NH_4H_2PO_4$, gelatin glutaraldehyde, hydroxyapatite	Bioceramic composite MNs	After transdermal application to diabetic rats, the released insulin from bioceramic composite MNs had an efficient hypoglycaemic effect and a greater plasma insulin level for a prolonged period compared to subcutaneous injection	(Yu et al. 2017b)
Insulin	3-Aminophenylboronic acid, N-hydroxy succinimide, sodium hyaluronate, sodium alginate, rhodamine B, calcium chloride, fluorescein isothiocyanate isomer- I, streptozotocin, isoflurane, polydimethylsiloxane	Polymer MNs patches	Encapsulated insulin in MNs revealed persistent hypoglycaemic effect in diabetic mice, with relative pharmacologic availability of $90.5 \pm 6.8\%$ and relative bioavailability of $92.9 \pm 7.0\%$, as compared to the subcutaneous injection route with the same insulin dose	(Yu et al. 2017c)
Insulin	Poly- γ -glutamic acid (PGA), fluorescein 5(6)-isothiocyanate, γ-PGA hydrogel powder, blue-dextran, phosphate buffered saline	Poly- γ -glutamic acid MNs	Innovative MN device design allowed for fast and easy self-administration of protein drugs and was found to be a suitable alternative to hypodermic needles	(Chen et al. 2015)
Insulin	Cetyltrimethyl ammonium bromide, polyvinylpyrrolidone, tetraethyl orthosilicate, 3-aminopropyl-tri-ethoxysilane, fluorescein isothiocyanate, glucose oxidase, 4- dimethyl-aminopyridine, carbonyl-diimidazole, anhydrous dichloro-methane, streptozotocin, poly (methyl methacrylate)	Insulin loaded and H_2O_2-responsive mesoporous silica nanoparticle (MSN)	Developed glucose-mediated and H_2O_2-responsive MN systems were found to have a potential diabetes application	(Xu et al. 2017)
Insulin	Fresh mulberry silkworm cocoons, proline, streptozotocin	Composite silk fibroin MNs	The drug-loaded silk MN patches might act as potential delivery systems for diabetes treatment	(Zhu et al. 2020)
Insulin	Poly (vinyl alcohol), polyethyleneimine, poly (lactic-co-glycolic acid), glucose oxidase, fluorescein isothiocyanate, streptozotocin, dihydrate, poly (methyl methacrylate)	Porous polymer-coated MNs	The proposed MNs can be used to deliver insulin in a regulated, glucose-responsive manner	(Ullah et al. 2020)
Insulin	Soybean lecithin, cetyltrimethyl ammonium bromide, sodium dodecyl sulfate, streptozotocin, urethane	Nanovesicles	This method used nanovesicles to deliver peptides with high molecular weights in a non-invasive manner	(Chen et al. 2009)
Insulin	Polystyrene-block-poly (tert-butyl acrylate), polystyrene-block-poly (acrylic acid)	Bullet-shaped double-layered MNs	Prolonged insulin release from swellable MN patches, resulted in a gradual reduction in blood glucose levels	(Seong et al. 2017)

Table 2 (continued)

Drug	Excipients	Dosage form	Outcome and significance	Reference
Insulin	Methyl methacrylate, benzoyl peroxide, poly (vinyl alcohol), polydimethyl-siloxane, rhodamine B, fluorescein-isothiocyanate, streptozotocin	Tip-hollow and tip-dissolvable MNs	For transdermal drug delivery, the tip-dissolvable MN arrays are a potential medical device	(Ye et al. 2020)
Metformin	Poly (vinyl pyrrolidone), poly (vinyl alcohol), streptozocin, potassium, ferricyanide, sucrose, rhodamine 6G, lauric acid, anti-IL-1 alpha (ab7632), anti-IL-6, goat anti-mouse secondary antibody	Near-infrared light-triggered and separable MNs	When compared to conventional subcutaneous injections, metformin-loaded MNs had a better hypoglycaemic effect, minimal toxicity, and poor inflammation reaction	(Liu et al. 2020)
Metformin	Poly (methylvinylether /maleic acid), poly (ethylene glycol)	Hydrogel-forming MN patch	Hydrogel-forming MNs represented a promising technology that could be used for transdermal delivery of drugs with high oral doses	(Migdadi et al. 2018)
Insulin	Gelatin, genipin, polylactic acid, polydimethylsiloxane, streptozotocin	Rapidly separating genepin-crosslinked gelatin (MNs) mounted on polyvinyl alcohol-coated polylactic acid MNs (RS-PGC-MNs)	The fabricated RS-PGC-MNs kept insulin levels within therapeutic ranges for a long time	(Chen et al. 2018b)
Insulin	Polydimethylsiloxane, polyvinylpyrrolidone (PVP), carboxy-methylcellulose sodium salt, lissamine green B, bovine serum albumin, fluorescein-5(6)-isothiocyanate	PVP MNs	The PVP-based MN patch allowed for quick and easy self-administration	(Lee et al. 2017b)
Insulin	Gantrez® AN-139, copolymer of methylvinylether and maleic anhydride, isoflurane	Dissolving polymer MNs	Use of a polymeric MN system helped protein drugs to maintain their structural integrity and biological activity while allowing for rapid delivery through skin	(Migalska et al. 2011)
Insulin	Conjugated linoleic acid (CLA), carboxymethyl chitosan (CMCS), arginine (Arg), CLA-CMCS-Arg (CCA) polymer, sodium pentobarbital, streptozotocin	Polymeric nanoparticle	CCA-nanoparticle paired with solid MNs could provide an effective and painless transdermal insulin delivery system by allowing for regulated release and self-administration	(Zhang et al. 2020a, b)
Insulin	Dodecyl amine, 3-aminopropyltriethoxy-silane, calcium nitrate tetrahydrate, tetraethyl orthosilicate, glucose oxidase, fluorescein isothiocyanate, zinc acetate dihydrate, streptozotocin	Insulin-loaded and zinc oxide quantum dots capped mesoporous bioactive glasses (MBGs) integrated with MNs	MBGs-ZnO complexes-based MNs showed great potential for diabetes treatment	(Xu et al. 2018)

Table 3 Published patent literature about bacterial meningitis therapies

Patent name	Patent number	Applicant	Publication date	Reference
Patch loaded with dual-sensitive vesicles for enhanced glucose-responsive insulin delivery	US20200330562	North Carolina State University	22.10.2020	(Zhen and Jicheng 2020)
Prussian blue microneedle electrode for blood glucose monitoring, preparation method thereof, blood glucose monitoring patch and preparation method thereof	CN110558993	University of Science and Technology of China	13.12.2019	(Chenggang et al. 2019)
Glucose-responsive insulin delivery system using hypoxia-sensitive nanocomposites	TNP/2017/000439	North Carolina State University	12.04.2019	(Zhen and Jicheng 2019)
Glucose-responsive insulin delivery system using hypoxia-sensitive nanocomposites	ID2018/06279	North Carolina State University	29.06.2018	(Zhen and Jicheng 2018a)
Patch loaded with dual-sensitive vesicles for enhanced glucose-responsive insulin delivery	WO2018085809	North Carolina State University	11.05.2018	(Zhen and Jicheng 2018b)
Glucose-responsive insulin delivery system using hypoxia-sensitive nanocomposites	US20180110841	North Carolina State University	26.04.2018	(Zhen and Jicheng 2018c)
Glucose-responsive insulin delivery system using hypoxia-sensitive nanocomposites	PH1/2017/501910	North Carolina State University	05.03.2018	(Zhen and Jicheng 2018d)
Glucose responsive insulin delivery system using hypoxia-sensitive nanocomposites	IN201727037788	North Carolina State University	26.01.2018	(Zhen and Jicheng 2018e)
Glucose-responsive insulin delivery system using hypoxia-sensitive nanocomposites	CN107530296	North Carolina State University	02.01.2018	(Zhen and Jicheng 2018f)
Glucose-responsive insulin delivery system using hypoxia-sensitive nanocomposites	NZ736578	North Carolina State University	27.10.2017	(Zhen and Jicheng 2017)
Glucose-responsive insulin delivery system using hypoxia-sensitive nanocomposites	WO2016172320	North Carolina State University	27.10.2016	(Zhen and Jicheng 2016)
Built-in non-verbal compact instructional device integratable to applicator	JP2015171546	Nanomed Devices Inc	01.10.2015	(Bai 2015)
Systems and methods for intradermal delivery of therapeutics using microneedles	US20140350514	NanoPass Technologies Ltd	27.11.2014	(Levin 2014)

microneedle fabrication can be used, and manufacturing approaches can be upgraded. These materials must have appropriate mechanical strength and skin adherence, as well as be free of harmful degradation products. Materials generated from nature are also excellent possibilities. Another research area is to equip microneedles with unique features that allow them to adapt to increasingly complex functional prerequisites. Multi-responsive microneedles, for example, can deliver medications in a controlled manner whereas breathable microneedles can enhance skin comfort. In addition to wound-healing patches and 3D cell culture chips, microneedles can also be used in a variety of different biomedical applications. Furthermore, microneedles are frequently overlooked when compared to popular therapeutic technology. The results of biomarker detection obtained using microneedles should be compared to those obtained using conventional methods to assess the accuracy and efficiency of microneedle-based detections. Despite the increasing scientific advances in the field of microneedles, there is still a significant gap between academic research and industrial products. This is reflected in the restricted number of microneedle products available, all of which have basic characteristics (Zhang et al. 2020a, b). Several novel and fascinating MN concepts have recently been developed, all of which have the potential to be very useful in the future. Biodegradable polymer MNs, for example, have recently been developed and characterised. Polymer needles have the benefit of being far less expensive to manufacture than silicon needles, and they should not cause any harm if they break in the skin because they are biodegradable. This research focuses on biocompatible and biodegradable polymer MNs, which are intended to enhance safety and manufacturing efficiency (Chatterjee and Davies 2015). With the increasing variety of MNs, a comprehensive set of tests that can be used to examine all needles should be suggested. Preclinical testing (in vivo studies in animal models), clinical tests (to assess pain, inflammation), mechanical testing (to assess characteristics such as margin of safety), and fluidic flow testing (e.g. fluid pressure needed for particular flow rate) should all be included in this list. This would aid in not

Table 4 Current clinical status of ongoing trials based on applications of microneedles in glucose monitoring and treatment of diabetic conditions using microneedle-based drug delivery systems

Study title	Sponsor	NCT no	Phase	Study type/participants/allocation/ intervention model
Insulin delivery using microneedles in type 1 diabetes	Emory University	NCT00837512	Phase 2 Phase 3	Interventional/ 16/ randomized/ crossover assignment
Enhanced epidermal antigen specific immunotherapy trial-1 (EE-ASI-1)	Cardiff University	NCT02837094	Phase 1	Interventional/ 8/ NA/ single group assignment
Glucose measurement using microneedle patches (GUMP)	Emory University	NCT02682056	NA	Interventional/ 15/ NA/ single group assignment
Pharmacokinetic comparison of intradermal versus sub-cutaneous insulin and glucagon delivery in type 1 diabetes	Massachusetts General Hospital	NCT01684956	Phase 2	Interventional/ 20/ randomized/ crossover assignment
Pharmacokinetics/dynamics of basal (continuous) insulin infusion administered either intradermally or subcutaneously	Becton, Dickinson and Company	NCT01061216	Phase 1 Phase 2	Interventional/ 20/ randomized/ crossover assignment
Multi-day (3) in-patient evaluation of intradermal versus subcutaneous basal and bolus insulin infusion	Becton, Dickinson and Company	NCT01557907	Phase 1 Phase 2	Interventional/ 23/ randomized/ crossover assignment
A pilot study to assess the safety, PK and PD of Insulin injected via MicronJet or conventional needle (MicronJet)	NanoPass Technologies Ltd	NCT00602914	Early phase 1	Interventional/ 23/ non- randomized/ crossover assignment
Safety and efficacy of ZP-glucagon to injectable glucagon for hypoglycemia	Zosano Pharma Inc	NCT02459938	Phase 1	Interventional/ 16/ randomized/ crossover assignment
Suprachoroidal CLS-TA with intravitreal Aflibercept versus Aflibercept alone in subject with diabetic macular edema (TYBEE)	Clearside Biomedical, Inc	NCT03126786	Phase 2	Interventional/ 71/ randomized/parallel assignment
Suprachoroidal injection of CLS-TA alone or with Aflibercept in subjects with diabetic macular edema (HULK)	Clearside Biomedical, Inc	NCT02949024	Phase 1 Phase 2	Interventional/ 20/ non- randomized/ parallel assignment

only objectively comparing MNs, but also in selecting the best MNs for each application (Teo et al. 2006; Liu et al. 2012). Conclusively, it has been manifested that MNs have a lot of potential in biomedical applications.

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Author contribution.

IZ, SS, and TB: conceived the study and wrote the first draft of the paper; NS, TN, VS, and SF: data compilation; IZ, NKF, and SB: figure work; AAH, SNW, and CVDLA: editing; LA and SBU: proofread.

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Declarations

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