Recent Advances of Diabetic Screening and Treatment

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Abstract. Blood glucose lever monitoring is an essential routine work for patients who are diagnosed with diabetes including type I and II. Insulin therapy plays a crucial role in treatment for both types of diabetes, whereas insulin delivery system has limited the capacities of insulin-loading, even worse, is not able to manufacture easily. Existing machines for measuring blood glucose are cumbersome, in addition, people need an injection of insulin for blood glucose regulation. The delivery route imposes restrictions on portability, the transdermal alternative seems favorable for the drug delivery. Naked-eye glucose monitoring base on colloidal crystal (GCC)-MN, aim to enhance health, improve portability and minimize invasiveness. This review discussed the sophisticated painless device named colloidal crystal (GCC)-MN patch for diabetes treatment and the process of glucose monitoring and responsive insulin release.

Keywords: Diabete; monitor; microneedle; transdermal.

1. Introduction

Diabetes affects over 450 million people worldwide, which is a kind of metabolic diseases characterized by hyperglycemia caused by defective insulin secretion, insulin resistance, or both. Perennial hyperglycemia causes chronic damage and dysfunction of various tissues, especially eyes, heart, kidney, blood vessels and nerves, causing irreversible damage even organ failure. It is reported that genetic heterogeneity should be responsible for both type 1 and 2 diabetes, and the fact that diabetes is an inherited disease means that it runs in families. Type 1 diabetes, also known as juvenile, insulin-dependent, childhood-onset diabetes, usually begins in childhood. Obesity due to overeating and reduced physical activity is a main risk factor for type 2 diabetes.[1]

Blood glucose monitoring is a regular inspection of blood glucose levels and can be carried out to better manage changes in blood glucose of people with diabetes. Insulin is subcutaneous injected traditionally. Although effective, this mode of delivery has certain limitations, including pains and time limit. At present, the mainstream device is called ‘glucose meter’ which caused injury to human skin. Patients need to have finger pricked by the device and squeeze few drops of blood to the edge of the test strip, then the device will determine the concentration of blood glucose by some chemical reactions on the strip, which shows the invasiveness. More importantly, before patients use the glucose meters, they need to differentiate which types of diabetes they get considering on type 1 and2 diabetes have different ways to detect. For type 1, patients need to avoid eating meals and snacks before testing and also refrain from exercising due to it may change their blood glucose significantly before detection possibly during the night. Additionally, for type 2, patients may check before each meal and bed and make sure the tests are after two hours from each meal and bed which are troublesome.

The discovery and development of insulin as a diabetes treatment dates back to the 19th century. To date, insulin replacement is still crucial in the treatments of type1 and type2 diabetes and resulting in good glycemic control. Fluctuations in blood glucose levels are synchronised with endogenous insulin secretion from the beta cells of the pancreas, thereby minimising hyperglycaemia and hypoglycaemia in healthy individuals. Circulating nutrients are the most important regulators of insulin secretion, especially glucose. During fasting, insulin secretion is maintained at sufficient insulin levels, thus inhibiting the release of hepatic glucose, so that blood glucose concentrations are maintained at normal levels. While exogenous insulin replacement methods are designed to offset endogenous insulin secretion, the daily dose of insulin injections must be determined by the individual's physiological status and lifestyle, including stress and daily changes in dietary intake which reveals the limitations and invasiveness.

At present, the convenient and practical traditional invasive blood glucose testing technology is the mainstream, so both hospital blood glucose meters and home blood glucose meters use the method of blood collection before in vitro analysis for blood glucose testing. Although the results are accurate, those methods are not suitable for diabetic patients continuous monitor due to the cumbersome process, long testing time and large samle of venous blood. Scientists are desperately eager for devoting themselves to invent a new type of non-invasive blood glucose monitoring called colloidal crystal microneedle patch (GCC)-MN. The patch is designed to support stimulating the sensing and reporting for the insulin delivery using a polymeric core. The GCC-MN patch is loaded with Insulin and glucose-responsive polymeric matrix prepared by in situ photopolymerization to regulate blood glucose in insulin-defined diabetic patients, could transfer the information of the glucose concentration to different recognizable colors with naked-eye and release insulin by the changes of glucose concentration through the endermic microneedle.

2. Solid MN arrays

Solid MN arrays were the first generation of MN array designed to be developed in 1998, and they use a 'poke-patch' approach. This two-step design philosophy has been widely used for transdermal administration of several medicines, including insulin. McAllister et al., widely recognized as the pioneers in this field, produced solid silicon MN arrays to enhance in vitro insulin administration over human skin. The beginning of the period, they demonstrated that the solid MN arrays deliver therapeutically meaningful insulin dosages capable of fulfilling the basal requirement of many diabetics. Martanto et al. used solid metal MN arrays to discover a comparable effect on diabetic rats. The level of blood glucose were reduced by up to 80% in this case. These exploratory investigations demonstrated that the MN arrays have considerable potential in improving diabetes control because to their painless delivery. To increase the commercial feasibility of the solid MN array device, which was used to administrate insulin, Li et al. constructed a novel biodegradable solid MN array comprised of polyethylene lactic acid. The level of blood glucose in diabetic mice model were reduced to 29% of the starting level after 5 hours, but blood glucose levels in SC injections declined swiftly to 19% after 90 minute before gradually climbing to 100% after another 90 minute. This indicates that solid MN arrays can deliver insulin across the skin painlessly and efficiently for a longer duration than the traditional methods. Despite the solid MN-mediated delivery systems show many considerable advancements, a number of critical problems remain. This includes the inconvenient two-step application process, appropriate method to store the insulin-containing formulation and prevent microbial outbreak, the need for a higher drug loading to achieve the same hypoglycemic effect as a SC injection, and controlling the dose of insulin delivered. As a result, metal and silicon may not always be the best options on the material. There are many worries that non-biodegradable materials may pose hidden danger when injected into the patients` skin. Safety concerns include silicone-related granulomas and instances of solid MN array points remaining in the skin following solid MN array excision. Nonetheless, these preliminary research with solid MN arrays laid the groundwork for creating more complicated novel MN systems, as mentioned below.[2]

3. Coated MN arrays

Typically, the coated MN arrays are used to the administration of very powerful, low-dosage macromolecules, such as vaccinations. This is mostly owing to the design's restricted loading capacity. As a result, there search employing insulin based on coated MN arrays is limited, and as far as we know, just one *in vivo* investigation using a diabetic mouse model has been completed. Several approaches are often used in the fabrication of the coated MN arrays including dipping, gas jet drying, spraying, and ink jet printing. Ross et al. coated insulin onto metal MN arrays using an ink jet printing procedure and a variety of polymers such as gelatin, poly (2-ethyl-2-oxazoline) (POX), polyvinyl caprolactame-polyvinyl acetate-polyethylene glycol (SOL) and trehalose. Despite the fact that this

resulted in homogeneous insulin-polymer layers, gelatin and POX had a negative influence on insulin stability, with the investigators identifying probable conformation alterations in the peptide's secondary structure by circular dichroism analysis. Insulin release in vitro utilizing pig skin revealed that SOL-insulin performed best, releasing its whole payload after 40 minutes. Pere used a 3D printing stereolithographic approach to produce MN arrays with varied patterns in a similar work. The insulin formulations containing mannitol, trehalose, or xylitol were then deposited on the MN array surface using ink jet printing. Interestingly, all of the coated formulations employed in this work showed the same in vitro release characteristics for cone and pyramid shaped 3D printed MN arrays, with around 90% to 95% insulin released in 30 minutes. This team also investigated the impact of this fast release profile in a diabetic mice model. In this investigation, the positive control (SC injection) induced a rapid increase of serum insulin concentration, as predicted, lowering serum glucose to around 30% of its starting value after 60 minutes. Interestingly, at the same lowered blood glucose rate as the SC injection were observed in the 3D printed MN array group, with comparable glucose levels after 60 minutes. Furthermore, across the 4-hour testing period, this MN array device outperformed SC injection in terms of steady-state hypoglycemic impact. This demonstrated that 3D printing would be a useful tool to deliver insulin rapidly. This coated MN approach offers patients a more user-friendly, one-step application of transdermal insulin delivery process compared to solid MN arrays that require skin preconditioning. The quantity of drug/insulin formulation that can be coated (and indeed, uniformly spread) throughout the surface of the MN array itself is a technical problem of this delivery approach. The loading capacity of such an array is limited due to the tiny size of the needles. Dosing is typically restricted to microgram (mm) increments. As previously stated, medication amount and needle strength should be in balance. The mechanical strength of MN arrays may be altered by increasing the quantity of coated insulin. Perhaps, the coated MN array device bearing more concentrated form of insulin, smaller therapeutic doses could be achieved.[3]

4. Dissolving MN arrays

Those decomposed MN arrays enclose their payloads in a soluble matrix, which is often made-up biodegradable polymer including carbohydrate. When applied to the skin, interstitial fluid (ISF) causes the MN array to disintegrate, causing its contents releasing into the superficial dermal microvasculature system. Due to this self-disabling device, there is no chance of renew needles and no need for sharps disposal, which is a problem with solid, coated, and hollow MN arrays.

Dissolved MN arrays are typically made of low-cost polymeric materials that can be processed at room temperature. For example, chondroitin sulfate, hyaluronic acid and polygamma-glutamic acid have been employed to create insulin-loaded dissolving MN arrays. Liu et al. created a dissolving MN array carrying 0.13 IU or 0.44 IU of insulin based on HA, which led in a 43% and 88% drop in serum glucose levels, respectively. Migalska et al. created MN arrays by poly-methylvinylether maleic anhydride combined with insulin in a similar investigation. In diabetic rats, this increased insulin transport and gave a dose-dependent hypoglycemic effect. However, the total quantity of insulin administered across the skin accounted for 40% to 55% of the initial drug loading. As a consequence, the MN arrays in this investigation generated 40-fold lower hypoglycemic impact than the SC group. This emphasized that the difficulties in delivering bigger biomolecules, with distribution frequently restricted to the medication put in the needles, resulting in unwanted drug waste. As a result, a two-step manufacturing technique has been developed in which the biomolecule is exclusively stored in the needles. Ling et al. created another starch and gelatin dissolving bilayer MN array with insulin-loaded needles and a drug-free baseplate. Importantly, after encapsulation and release from the MN arrays, the pharmacological activity of insulin was maintained. Pharmacokinetic and pharmacodynamic results in rat models, which received insulin-loaded MN arrays and a SC injection, revealed a similar hypoglycemic effect. Ito et al. also created a two-layered dissolving MN array, which is made up of chondroitin sulfate needles with protamine sulfate insulin (PSI), intermediate-acting insulin and a drug-free chondroitin sulfate supporting baseplate. PSI was released

within 5 minutes after skin implantation from the MN array. The percentage of pharmacologic availability of PSI from the MN arrays was 100.2 9.8%, but no significant changes in hypoglycemic effects reported in rats as compared to a SC injection in vivo. Designing a MN system which insulin is rapidly dissolved and only loaded into the needle tips offers a great potential for bolus and mealtime insulin administration. Biodegradable polymers like as chitosan, amylopectin and carboxymethlycellulose can be employed for long-term insulin administration. Previous research has revealed, however, that these materials require high temperatures in processing, which reducing insulin stability. Liu et al provided a proposed solution to solves this which is encapsulate the insulin in microparticles. A two-layered dissolving MN array made of insulin-loaded CaCO3 microparticles and a poly (vinyl pyrrolidone) (PVP) matrix was created in this study.

The largest drop in serum glucose occurred after 120 minutes through SC injection (5 IU/kg) in diabetic rats. In contrast, after 4 to 5 hours after implantation of the dissolving MN array (20 IU/kg), a similar drop in serum glucose level was seen. The sluggish diffusion rate of insulin from the MN array was attributable to the gradual fall in glucose levels. The scientists also demonstrated that the MN array device-maintained serum glucose levels in a normoglycemic condition for twice in accordance with the SC control. Multiple daily insulin injections have been a standard diabetes care regimen across the world. Chen et al designed a single integrated MN array with different release kinetics to imitate the daily bolus release of insulin in this scenario. Chen et al. created the MN using gelatin or cross-linked gelatin, and a combination of cross-linked gelatin and hyaluronic acid in a single platform to provide three distinct insulin release profiles that may provide insulin on a post-breakfast, lunch, and supper trend. Streptozotocin (STZ)-induced diabetic mice model revealed that the produced device was not only rapidly responding to elevated glucose levels, but also rapid transdermal delivery of controlled release depots for basal-bolus combinatorial insulin release.[4]

5. Conclusion and perspective

In recent years, transdermal drug delivery systems, notably MN arrays, have received increased interest and recognition as a possible alternative for diabetes therapy due to the advantages they provide over invasive injection and daily oral dose forms. This research indicated that the MN arrays successfully administered a range of medicines used to treat diabetes at therapeutic levels. Furthermore, MN array designs have advanced greatly since their inception to include complex technologies like as reverse iontophoretic devices, glucose-responsive closed-loop delivery systems and coatings that release medicine only when activated by light or heat. This continuous and quick evolution from the first rudimentary MN array design has contributed to expand the technology's potential and eliminate many of the challenges connected with its initial use.[5]

Although the biopharmaceutical market has grown hugely, driven by the potential of the impossible disease before biopharmaceutical treatment, the challenge still exists to enable biopharmaceuticals to give full play to its market potential, these challenges must be overcome. For example, most biological drugs must currently be stored and transported under the "cold chain". This is expensive maintenance, which limits the potential of biological drugs in developing countries. This condition in these countries is not common. In the dry state, synthetic drugs in the MN array not only improve the chemical and physical stability of the drug, but also eliminate the need for cold chains. There may be many requirements for the MN array to give full play to its potential and obtain the approval of the regulatory authorities. These requirements have been summarized in other places, although these requirements are not only applied to the formula for treating diabetes drugs. These considerations include but not limited to the large -scale and large -scale production of the MN array, potential needs for sterile, MN array packaging and treatment, and long -term stability of drugs in MN array, especially biopharmaceuticals. It is worth noting that if the regulatory authorities believe that this is necessary, some companies can now use scalable methods to produce MN arrays under sterile conditions according to GMP standards. Three examples of such companies are LTS Lohmann, Kindeva and Fujifilm. MN arrays clearly have the potential to change how we administer medications

transdermally. However, their full potential in terms of market value and patient benefit cannot be achieved unless they are commercialized. To guarantee that the significant benefits of MN arrays balance the development costs, focused coordination between industry, academics, patients, and regulators will be necessary. Through PATH's "Centre of Excellence For Microarray Patches," this collaboration has already begun and is now happening.[6]

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