Microneedle-array patch system applications in diabetes

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Abstract. Diabetes is turning into a chronic disease with further improved drugs and more facilitated delivery systems coming out. An essential part of the drugs is insulin and its analogs that patients with diabetes use to control their blood glucose levels. The conventional treatments, like injection and open-loop (release are not responsive) transdermal delivery, are short of maintaining glucose levels in the expected range incurring risks of hypoglycemia. Nevertheless, closed-loop drug delivery shows high potential as its release response to glucose levels dynamically. In the transdermal delivery field, microneedle (MN)-array patch systems presented great capability in transdermal delivery and manipulation. So, the glucose-responsive MN-array patches that make progress in safety and convenience were drawing worldwide focus. This review provides an overview of the topic and presents some advanced outcomes.

Keywords: microneedle patch, responsive, insulin.

1. Introduction

Diabetes is a chronic disease incurred by either insulin-producing inefficiency or incompatibility in utilizing insulin. From 1980 the number of people with diabetes almost quadrupled from 108 million to 422 million in 34 years worldwide. No cure method exists for diabetes now, patients need to undertake lifetime drug control which involves daily injections, frequent blood glucose level checks, and hypoglycemia risks. Researchers are devoted to developing more easy-to-apply and safer drugs. Microneedles (MNs) patch is one popular formulation of them. MN patch is an array of tiny needles. When applied to the skin it creates physical pathways through the stratum corneum. This enables the MN patch to achieve improved transdermal drug delivery. The lengths of needles are determined inside a fine range from 0.10mm to 3.00mm which enables a painless administration while effectively delivering drugs. In recent years, a concept, “smart release patch” was put forward suggesting an environment-sensing MN patch is more capable in regulated drug delivery and self-control release. In the case of diabetes, insulin and its analogs are now widely used, and if administered improperly like overdose it raises risks of generating hypoglycemia. To avoid improper drug use, patients have to examine blood glucose levels, which brings consequent cumbersome efforts.

With years of devotion, dedicated Researchers have successfully provided solutions. Categorizing them by their sensing elements, which always function as the core of the release behaviors, there are glucose oxidase (GOx) -based, PBA-based, and glucose transporter (GLUT)-based MN patches. To provide insight into glucose-responsive microneedles, this article presents instances in classes with their molecule-level mechanics, patch structures, delivery behaviors, and distinguishing features.

2. GOx-based glucose-responsive microneedle

Glucose oxidase has been widely utilized in glucose sensing, which converts glucose with the presence of oxygen into gluconic acid and H$_2$O$_2$ and generates an acid, hypoxic, and H$_2$O$_2$-rich local environment. Following this environmental change, several methods that are sensitive to either acid or hypoxic were applied to finally trigger the release of insulin. This conversion is completed in an enzymatic process, which contributes to its specificity and sensitivity. They also involve various media like HA, PVP, and MOF. In addition, Gu et al. [1] made a microneedle with embedded pancreatic cells which amplifies the stimuli of glucose. Wang et al. [2] made their microneedle with CAT making the elimination of H$_2$O$_2$ more effective.
2.1. GOx with pH-sensitive hydrogel

In history, the first glucose-responsive material was made by combining GOx, the sensing element, with pH-sensitive hydrogels, the constituting element. When a considerable rise happens in blood glucose level, the GOx converts glucose into gluconic acid. With a lowered local pH, the hydrogel will capture protons and turn into a higher charged state. This consequently generates a volume change of hydrogel as a glucose-triggered response.

Ishihara et al. [3] were the first to regulate insulin release with a glucose-sensitive membrane. The membrane was a combination of two related layers: a pH-responsive layer, a copolymer consisting of N, N-diethyl aminoethyl methacrylate (DEAEM), and 2-hydroxypropyl methacrylate (HPMA), and a GOx immobilized layer. The permeability of insulin will increase when glucose concentration rises. When the glucose is converted into gluconic acid in an enzymatic way, it decreases the pH of the matrix. The tertiary amino groups of the constituting DEAEM will capture the protons inducing a generation of aqueous pathways as water immerses into the matrix. Thus, the permeability of insulin through complex membrane is strengthened.

This modulated hydrogel membrane with GOx, however, is not capable enough to achieve smart insulin release or a closed-loop release as the insulin is able to permeate the membrane even in the absence of glucose and the increase in permeability happens since the very start of glucose concentration rises from 0, which is far from ideal characteristics that showing no insulin release in steady-state and only show response for the excessive blood glucose levels. Albin et al. [4] described the steady-state profile of glucose-responsive membranes with immobilized Gox in their mathematical model. To be specific, a model of the steady-state performance with phenol red is prepared which predicted qualitative changes of membranes. They believe it was able to accurately predict whether the pH change will be generated when a specific factor is changed. In addition, this model can correctly predict the profile of the plots of medium pH and oxygen tension.

2.2. GOx and hypoxia-sensitive vesicles at HA

The locally hypoxic environment also shows as a promising stimulus for insulin release in GOx-leading materials. Yu et al. gave the concept of the smart insulin patch and first demonstrated a prototype microneedle patch that takes hypoxia as the stimulus to trigger insulin release [5]. The glucose-responsive vesicles (GRVs) were formed through a self-assembly process. Insulin and GOx are buried in the core of the HS-HA vesicles. HS-HA was produced by combining hyaluronic acid (HA) with amine-functionalized 2-nitroimidazole (NI) through an amide bond.

Derived NIs induce hydrophobic properties to the part they are located at of the HA molecule. This enables the HS-HA self-assembly within an aqueous environment into GRVs encapsulating insulin and GOx. NI groups are supposed to be bioreduced into 2-aminoimidazole, a product with hydrophilic properties. When BGL rises, GOx efficiently converts the glucose into gluconic acid consuming oxygen. Then in lack of oxygen, the NI groups embedded inside the GRVs in the progress of self-assembly start to be bioreduced losing their hydrophobic property. This finally incurs the disassembly of vesicles releasing the insulin, which achieves regulated glucose-responsive release.

The GRVs are stable and show no considerable precipitation in 1 mO under 4°C. In an experiment on release behavior, GRVs were tested under a typical high blood glucose level (400 mg/dL), a normal blood glucose level (100 mg/dL), and a control level (0 mg/dL). In the typical high blood glucose level of 400 mg/dL glucose, the GRVs achieve a quick release of encapsulating insulins, whereas a relatively small amount of GRVs were triggered to release in 100 mg/dL glucose and virtually none in PBS.

2.3. GOx and hypoxia-sensitive vesicles at HA

Metal-organic frameworks (MOFs) are a class of materials that are made of coordination bonds between transition-metal clusters and organic linkers with highly crystallizable properties. The structure of MOFs is characterized by the kind of metal cluster, organic linkers, and molecule ratio and always shows porosity with extremely high specific surface area. The size of pores and 3
dimension structures can be fine-tuned to meet various requirements, which makes it a promising drug delivery medium. Zeolitic imidazolate frameworks (ZIF) are widely studied as a subcategory of MOF for controllable release. ZIF-8 consists of 2-methyl imidazolate and Zn\(^{2+}\) ions.

Yang et al. [6] designed a metal-organic framework (MOF)-based glucose-responsive microneedles. In their study cobalt-doped ZIF-8 was used as the frame loaded with insulin and GOx (Ins/GOx@Co-ZIF-8). These systems start with GOx catalysed glucose conversion creating a decreased pH in MOF structure and H\(_2\)O\(_2\) as well. The following step is the disintegration of ZIP-8 which features the ability to degrade under an acidic environment. In the degradation, both insulin and toxic H\(_2\)O\(_2\) were released, and the Co\(^{2+}\) ions doped in the framework catalyzed H\(_2\)O\(_2\) breaks into water and Oxygen. Excessive Co\(^{2+}\) ions would be absorbed by the base in which Co\(^{2+}\) ions were captured by forming metal complexes with EDTA-SiO\(_2\) nanoparticles.

The release behaviors of ins/GOx@Co-ZIF-8 under a series of glucose concentrations (0 mM, 1 mM, 5 mM, 10 mM, 15 mM) were tested and it presented a higher release rate and amount of insulin in higher glucose concentration, only a small part of insulin is released in 0 mM control group. In the switchable time-dependent insulin release test, concentration changed between 15 mM for high glucose level and 1 mM for low glucose level every 20 min and the released insulins in every shift were examined. The release proceeded in high glucose concentration and ceased in low concentration. This provided information for the possibility of release regulation.

Thanks to the great crystallizable characteristic, Ins/GOx@Co-ZIF-8 can be synthesized in a one-pot reaction. PVA was chosen for the matrix material. In preparation, Ins/GOx@Co-ZIF-8 and EDTA-modified SiO\(_2\) were mixed in PVA solution and formed shape through micromodling technology.

3. Phenylboronic acid (PBA)-based glucose-responsive microneedle

The PBA-based controlled-releasing system has been widely used for responsive insulin release. It shows advantages in wide selectivity that various stimuli are available and chemical modification that by changing molecule groups properties can be adjusted achieving.

3.1. PBA-decorated gold nanocluster

Zhang et al. [7] designed a kind of gold nanoclusters (GNCs) with PBA decorated. Gold nanoclusters (GNCs) have extremely tiny sizes (2-3 nm), excellent biocompatibility, and are readily available for surface modification. Gluconic-modified insulins were grafted on the surface of carriers at the end of PBA. These GNC-PBA-Ins complexes then were molded into MNs with polydimethylsiloxane (PDMS) as a matrix. The release was achieved by the replacement of glucose with grafted insulins.

The drug release profiles of the MN patches in multiple glucose levels were drawn. Solutions whose glucose levels are 5.5, 11.1, and 22.2 mM respectively were prepared. Each concentration was chosen matching the physiological blood glucose levels from healthy to diabetes. MNs showed a relatively smooth release profile in all tested glucose concentrations. Half of the insulins were released after 120min incubation.

The mechanical properties are part of the essential factor of successful MN patches. Proper shape and adequate mechanical strength are required for effective penetration through the skin. Morphology of MN-array patches was scanned and observed. Needles showed as well-shaped cones and the gold element in the needles, which was observed by energy-dispersive spectroscopy, were evenly distributed. In the mechanical strength test, the MN was evaluated by Young’s modulus. In comparison with MN materials without GNCs, Young’s modulus of 1 × GNCs/MN increased from 6.522 to 16.648 MPa, a ~ 250% improvement. The mechanical strength would conversely decrease when 1 × GNCs/MN changed to 5 × GNCs/MN. This outcome was accorded with previous research [8].
3.2. PBA-decorated dynamic covalent bonding method

Zhou et al. [9] designed a PBA-sensing dissoluble MN array that reacts to blood glucose concentration. There are two kinds of polymers were used, which are DMAA-co-PyPBA and diol-modified 4-arm PEG. DMAA-co-PyPBA had a web structure and pendant PBA motifs were linked to the polymer molecules. And diol-terminated four-arm PEG macromer would combine with PBA motifs into hydrogels that are capable of being fabricated into MN arrays.

PBA motifs were connected with diol by covalent bonding, and these bonds also play the role of sensing. PBA–diol chemistry is widely explored and used in preparing dynamic-covalent networks. When the glucose level changes, the level of crosslink changes in the PBA network. A higher glucose level brings a lower crosslink rate that makes the polymer turn into a less dense state. Trapped insulin were released according to the degree of decrosslink.

In the fabrication of MNs array, forming preformed hydrogels through the mold method is not feasible, and another proper approach is required. Attributes to its dynamic-covalent crosslink feature, hydrogels would deform filling space and defect by dynamic bond rearrangement under applied mechanical force. A fabrication method by centrifuging was developed, in which preformed gels were set on the top of the MN array mold, and through centrifuge not only bubbles were removed but needles were formed filling the mold.

In vitro, the release of insulin behavior of the MNs array showed a facilitated release under 400 mg/dL glucose than PBS as the control group. In the treatment of animal models, streptozotocin-induced rats, the microneedle patch successfully relieved hyperglycemia. The blood glucose of rats treated with MN patches dropped gradually throughout ~ 4h followed by normalizing between 180-200 mg/dL. And blood glucose of rats treated with insulin-excluding microneedle patches showed no trend to drop in 12h observation. These confirmed the MN patch can penetrate the skin and regulate blood glucose levels.

4. Conclusion

The article covers several specific glucose-responsive MN patch designs. The COx-based pH-driven hydrogel releases insulins as a consequence of loss in dense gel polymer molecules and following permeation aqueous phase. The COx-based hypoxia-driven vesicle releases insulins through dissipation, which is attributed to the shift of the inner molecule end from hydrophobic to hydrophilic. Because the minimum unit of release is a single vesicle, it is feasible to cease facilitated releasing when the glucose level decreases. The MOF method also functions in a pH-driven mechanism. MOF breaks off spreading insulins inside. It has one feature in simple fabrication, it can be prepared in a one-pot reaction, and one feature in H2O2 elimination by Co2+ that mingled into the frame. Other designs rely on catalase carried with MN, or the the catalase provided by the host. The GNC methods not only achieved high drug loads and good biocompatibility but also found an optimal concentration for better physical strength of MN. The dynamic covalent gel shows an improved specificity than the previous pH-driven one. And despite the requirement incurred by its unsolvable matrix, the relief of potent toxicity showed adequate value. All mentioned methods managed to regulate insulin release according to glucose levels lowering the risk of hypoglycemia.

Beyond the convenience embedded in the form of MN and the “close-loop” feature that highlights the great value of these designs, MN design is still in its infancy. All these advantages in safety and efficacy, however, all the outcomes were drawn from the bench on rodent animals instead of from the bed. Hence, the translation to clinical use is highly needed. There are barriers to the translation, for instance, the microenvironment of human dermal that is different from that of rodents and the very limited load capacity considering the application in the larger human body.

Some new advanced technology shows benefits that help the translations. Taking 3D printing as a powerful manufacturing method, more personalized or complex MN can be made [10]. And AI, machine learning, and deep learning were also involved in the 3D printing manufacturing, which helped to fine-tune the parameters and even predicted the release behaviors. Finite element analysis,
which simulates real physical processes, was used to solve structural characteristics, drug loading performance evaluation, and potential industrialization. More research has been done to facilitate the translation of the bench work to clinical use.

References


