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Microneedle Insulin Patches: A Novel Approach Using Osmotic Agents for Prolonged Therapeutic Effects

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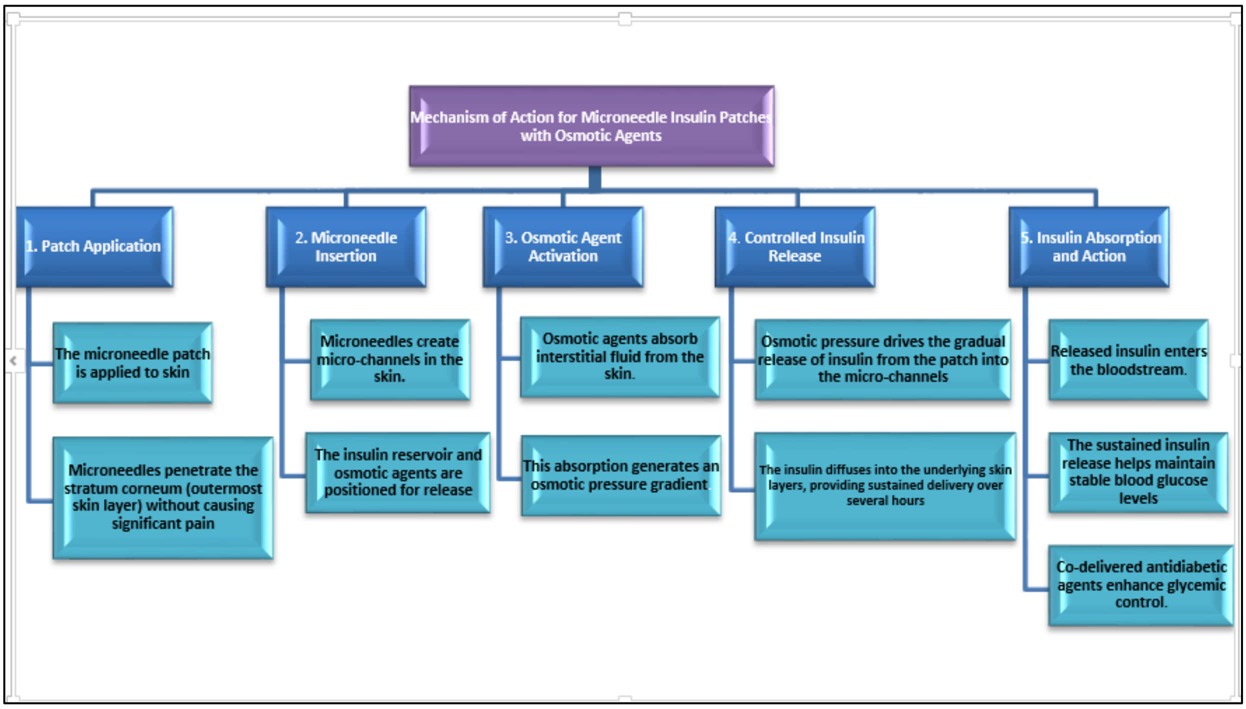
ABSTRACT

Diabetes management requires effective and sustained insulin delivery to maintain optimal glycemic control. This review article investigates the potential of microneedle-based insulin patches integrated with osmotic agents for achieving prolonged insulin release. Microneedle patches represent a minimally invasive and patient-friendly alternative to traditional insulin injections, potentially improving adherence due to their pain-free nature and ease of use. Incorporating osmotic agents within the patch formulation can regulate the rate of insulin diffusion, allowing for a sustained release profile that mimics the physiological basal insulin secretion more effectively Additionally, the co-delivery of a blood-sugar-lowering drug within the microneedle patch system aims to optimize therapeutic outcomes, combining insulin therapy with enhanced glucose regulation. This dual-action approach may reduce daily insulin dosages, mitigate the risks of hypoglycemia, and lower the burden of frequent blood sugar monitoring. The development of such a patch could revolutionize diabetes care by simplifying the treatment regimen, promoting better compliance, and enhancing the quality of life for patients. The review addresses the principles behind microneedle technology, the role of osmotic agents, and challenges in formulation, providing insights into future clinical applications and innovations.

Keywords: Microneedle patches, sustained release, osmotic agents, diabetes management, glycemic control.



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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistently high blood glucose levels, resulting from impaired insulin production, insulin resistance, or a combination of both. Effective management of diabetes is critical to prevent complications such as cardiovascular disease, neuropathy, and nephropathy.[3] Traditionally, insulin delivery via subcutaneous injections remains the primary method, but it is often linked to challenges like discomfort, needle phobia, and poor patient adherence, which can hinder effective glycemic control. In recent years, microneedle patches have emerged as a promising alternative for drug delivery.[4] These patches feature micro-sized needles that penetrate the outer skin layers, allowing for the direct delivery of therapeutic agents into the dermal microcirculation, bypassing both the gastrointestinal tract and first-pass metabolism.[5] Among the strategies to enhance microneedle patch efficacy, sustained-release formulations utilizing osmotic agents have shown great promise. These agents enable a controlled and prolonged release of insulin and other hypoglycemic drugs, potentially improving glycemic control and reducing the frequency of administration. This review aims to examine the design, mechanisms, and clinical implications of microneedle-based insulin patches incorporating osmotic agents, with a focus on recent advancements in the field to optimize diabetes management and patient outcomes.[6]

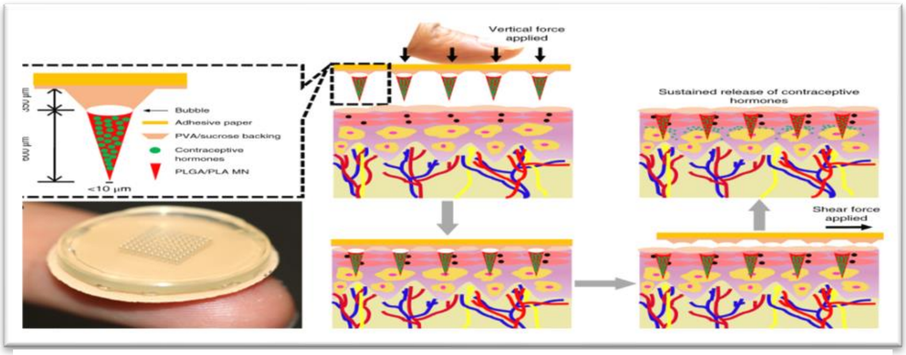

Figure 1: microneedle patch mechanism

1. Diabetes :

Diabetes is a chronic condition characterized by the pancreas's inadequate insulin production or the body's impaired ability to effectively utilize insulin. Insulin is a hormone responsible for regulating blood sugar levels in blood. Uncontrolled diabetes often leads to hyperglycemia, characterized by elevated blood sugar, which, over time, can cause significant damage to various body systems, particularly affecting the nerves and blood vessels. (17)

Type 1 diabetes mellitus (T1DM) is generally linked to a lack of insulin production caused by the destruction of pancreatic β-cells through T-cell-mediated autoimmunity. (18)

Type 2 diabetes mellitus (T2DM) is characterized by both insulin resistance and a decrease in insulin production. Studies have shown that life expectancy tends to be lower in individuals with T1DM compared to those with T2DM, mainly due to a higher occurrence of cardiovascular diseases and acute metabolic complications in the former group. (19)

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2. Microneedle Technology in Diabetes Management

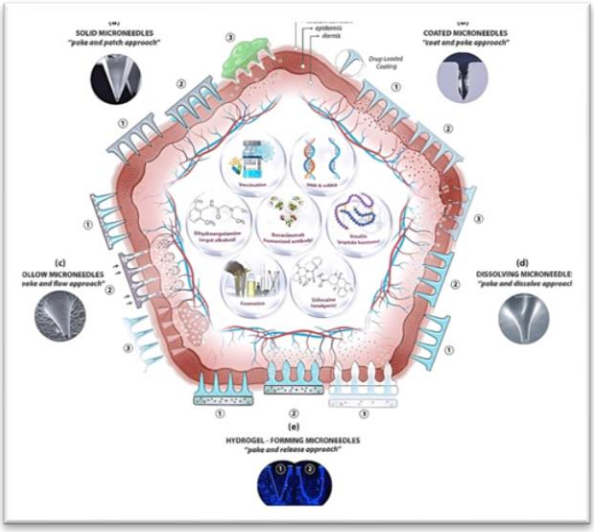


Figure 2: Types of Microneedle Design

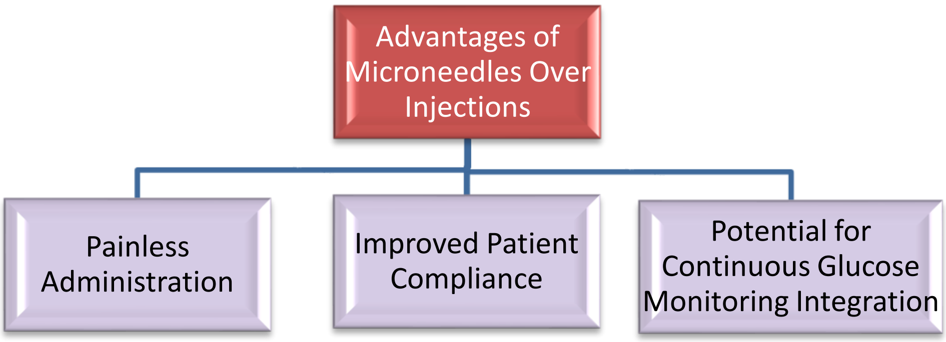
A} Microneedle Design

Microneedles are small, needle-like structures that penetrate the skin's outer layer without reaching the pain receptors, making them ideal for minimally invasive drug delivery. There are three types of microneedles:

a) Solid Microneedles: Primarily used for pre-treatment to create micro-channels in the skin. Drugs are applied post-treatment for enhanced transdermal delivery.

b) Hollow Microneedles: Feature a hollow bore, allowing for direct injection of liquid formulations, such as insulin, through the microneedle.

c) Dissolvable Microneedles: Made from biocompatible materials that dissolve in the skin, releasing the drug payload. They eliminate waste and improve patient safety by avoiding needle reuse.



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3. Osmotic Agents for Sustained Release:

- **Mechanism of Osmotic Release-**

Osmotic agents play a crucial role in controlling the rate of drug release from microneedle patches. These agents create an osmotic pressure gradient when exposed to bodily fluids, such as interstitial fluid. The gradient draws water through the skin and into the patch, causing the osmotic agent to swell and push the drug out of the microneedles at a controlled rate. This mechanism ensures a consistent and predictable drug release profile, crucial for maintaining stable blood glucose levels in diabetes management.

- **Common Osmotic Agents-**

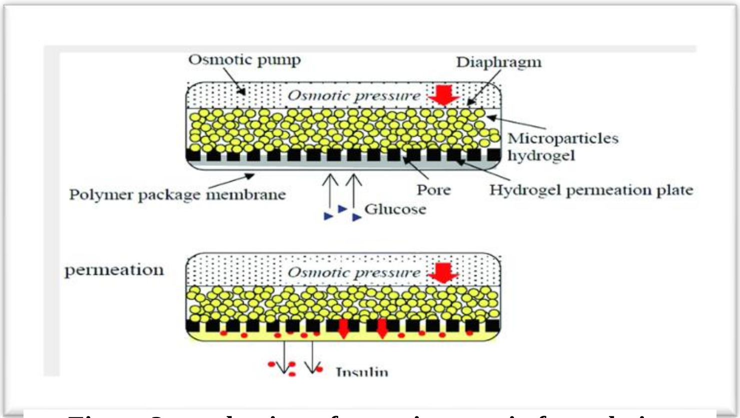


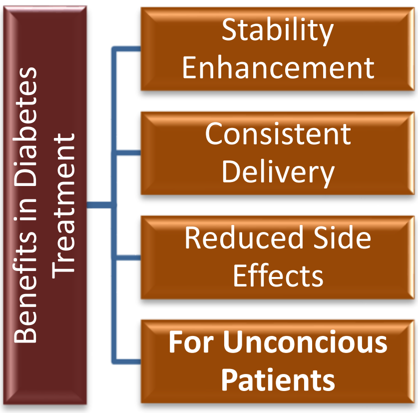
Figure 3: mechanism of osmotic agent in formulation

Several materials are commonly used as osmotic agents in drug formulations due to their hydrophilic properties and ability to modulate drug release. Some examples include:

- **Polyethylene Glycol (PEG)**: PEG is a widely used osmotic agent due to its ability to attract water and swell, facilitating controlled drug release. It is biocompatible and can be easily integrated into microneedle patch formulations.

- **Sodium Chloride (NaCl)**: Acts as an osmotic agent by creating a high osmotic pressure gradient, drawing fluid into the patch for controlled drug delivery.

- **Sorbitol and Mannitol**: These sugar alcohols are also used for their osmotic properties and are often combined with other agents to fine-tune the drug release profile.



4. Method of preparation and Formulation of a Combined Insulin-Drug Patch

A) Rationale for Combining Insulin with Other Drugs

Combining insulin with adjunct medications such as metformin, DPP-4 inhibitors, and GLP-1 receptor agonists offers a synergistic approach to managing diabetes. These adjunct drugs can enhance glycemic control through distinct mechanisms:

a) Metformin reduces hepatic glucose production and improves insulin sensitivity, working in conjunction with insulin to lower blood glucose levels effectively (11).

b) DPP-4 Inhibitors prolong the action of inserting hormones, promoting insulin secretion in response to meals, which helps mitigate postprandial hyperglycaemia (12).

c) GLP-1 Receptor Agonists stimulate insulin release, slow gastric emptying, and reduce appetite, thereby controlling both fasting and postprandial glucose levels (13).

"The synergistic effect of this combination therapy enables a decrease in insulin dosages, thereby mitigating the risk of hypoglycemia and facilitating improved glycemic control."

Figure 4 : selection of drug criteria for microneedle insulin patch

5. Potential Benefits and Challenges

A. Advantages of the Combined Patch System

1. **Improved Glycemic Control -** The integration of insulin with adjunctive agents such as metformin or GLP-1 receptor agonists enhances glycemic control by targeting multiple pathways in glucose metabolism. This synergistic effect allows for more effective management of blood sugar levels, which can lead to better long-term outcomes and a reduced risk of diabetes-related complications (14).

2. **Reduced Dosing Frequency-** The sustained release mechanism of microneedle patches allows for prolonged action, potentially decreasing the need for multiple daily injections. This improvement in administration frequency may enhance patient compliance, as the burden of frequent injections is alleviated (7).

3. **Minimized Side Effects –** The controlled release of drugs can lead to more stable plasma concentrations, thereby minimizing fluctuations that could result in hypoglycemia. By maintaining more consistent drug levels, patients are less likely to experience adverse effects associated with peaks and troughs in blood glucose (13).

B. Challenges in Formulation

a) Stability of Insulin and Drug in Patch Form

One of the primary challenges is ensuring that both insulin and the adjunct drug remain stable and effective during storage and use. Factors such as temperature, humidity, and light exposure can degrade these compounds, necessitating the development of robust formulation strategies to preserve their efficacy (11).

b) Patient –Specific Variability

Individual patient characteristics, such as body mass, skin thickness, and metabolic rate, can affect the absorption and efficacy of the patch. This variability requires personalized approaches to dosing and release profiles to optimize treatment outcomes for diverse populations (9).

c. Regulatory Hurdles

Navigating the regulatory landscape can pose significant challenges for the approval of combined drug delivery systems. Ensuring that safety and efficacy standards are met requires comprehensive clinical testing and adherence to stringent guidelines, which can delay market entry (10).

6. Future Prospects

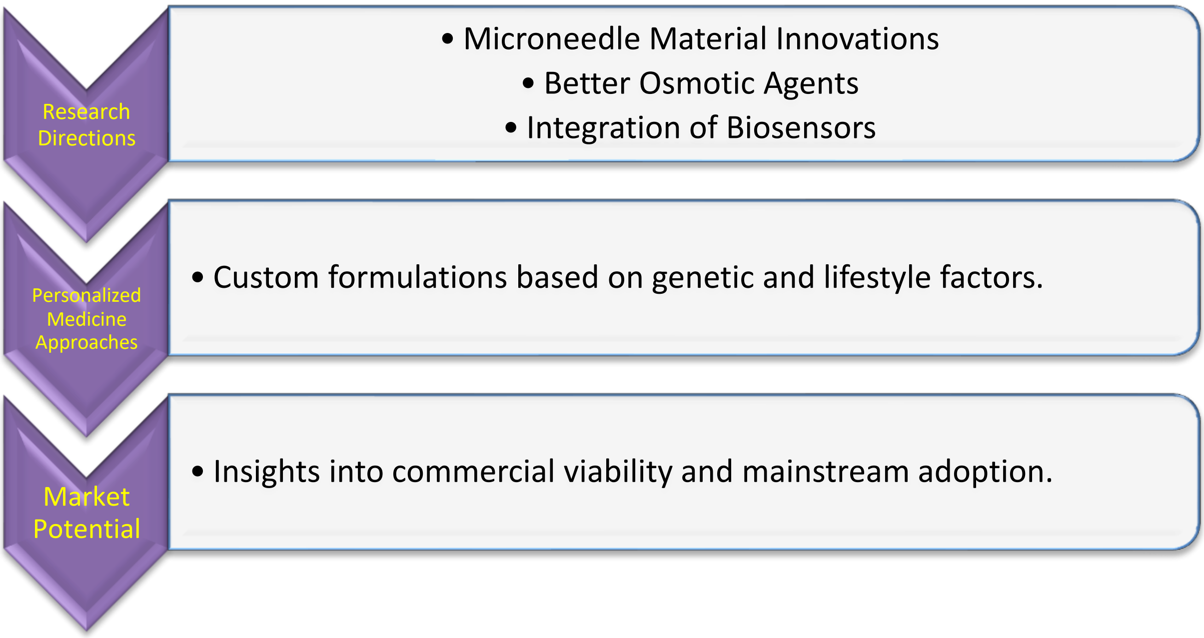


Figure 5: Future development in microneedle insulin patches

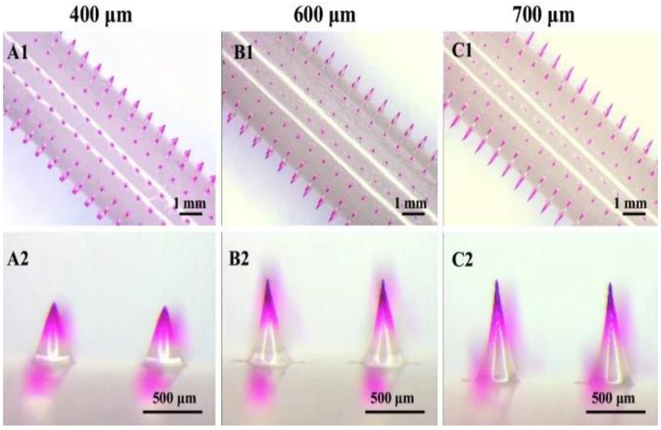


Figure 6 : Size Ranges in formulation of microneedle patches

7. Impact of Microneedle insulin patches –

The potential medical significance on study of microneedles may reduce pain and apprehension related with insulin delivery. With pain, anxiety, and fear of needles being the main reason for noncompliance among diabetes patients, we believe microneedles can provide a means to increase patient compliance. Integration of the microneedle device into a compact, wearable patch format improves patient compliance by reducing discomfort and inconvenience associated with traditional delivery systems. Overall improved patient compliance would ultimately lead to reduced healthcare costs for diabetes patients with potential lower frequency of hypo- and hyperglycemic events and related hospitalizations. The convergence of microneedle-based glucose monitoring and insulin delivery holds promise for a revolutionary, closed-loop microdevice. Our study brings us closer to realizing this vision, with the potential for improved glycemic control, enhanced patient comfort, and reduced complications. This innovation could significantly impact diabetes management.(15)

➢ **Discussion:**

microneedle insulin patches combined with adjunctive drugs and osmotic agents have the potential to significantly enhance diabetes treatment strategies. On-going investigations into materials, formulations, and real-time monitoring will play a critical role in realizing the full potential of this promising technology.

➢ **Conclusion**

Microneedle insulin patches, particularly those enhanced with osmotic agents for sustained release, represent a transformative advancement in the management of diabetes. By integrating insulin with adjunct hypoglycemic medications, such as metformin or GLP-1 receptor agonists, these patches can deliver a synergistic therapeutic effect, leading to improved glycemic control and enhanced patient comfort. The potential for reduced dosing frequency associated with microneedle patches may significantly increase patient compliance, a crucial factor in effective diabetes management. Moreover, the ability to tailor formulations to individual patient profiles through personalized medicine approaches holds promise for optimizing treatment outcomes. This customization can account for factors such as genetic variations and lifestyle, ensuring that each patient receives the most effective therapy while the prospects for microneedle insulin patches are promising; challenges remain, particularly regarding the stability of the combined formulation and the need for thorough regulatory assessments. Continued research and development in this field could lead to innovations that overcome these obstacles, ultimately revolutionizing diabetes management and improving the quality of life for millions of patients globally.

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