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Original Article

Transdermal Drug Delivery Systems in Diabetes Management: A Review

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ABSTRACT

Diabetes mellitus is a long-term disease that happens when the pancreas does not make enough insulin, or when the body cannot use the insulin properly. More than 415 million people in the world have diabetes, and this number may reach 642 million by 2040. The World Health Organization (WHO) says that by 2030, diabetes will be the seventh leading cause of death. Most people with diabetes are treated with insulin injections or tablets, but these treatments are sometimes hard for patients to follow regularly. In recent years, scientists have started focusing on transdermal systems – special patches or devices that deliver medicine through the skin. These systems have many benefits compared to injections and tablets. Studies show that medicines given through the skin are better absorbed because they do not pass through the liver first. They also release the medicine slowly over time, which helps keep blood sugar levels steady and reduces the need to take medicine many times a day. This makes it easier for patients to follow their treatment and improves their overall health. In short, using skin patches for diabetes treatment is a new and promising method that can make diabetes control easier and more effective.

Keywords: Transdermal, Diabetes, Antidiabetic, Insulin, Drug delivery system

INTRODUCTION

Diabetes mellitus is a long-term illness where the amount of sugar (glucose) in the blood becomes too high. This happens because the body does not make enough insulin. If diabetes is not treated, it can cause serious health problems like stroke, heart disease, or even death. Type 2 diabetes is more common than type 1. About 425 million people in the world have diabetes. According to the World Health Organization (WHO), diabetes cases have gone up to 4.7%, and it may become the seventh biggest cause of death in the world by 2030.Insulin is very important to control diabetes. In type 1 diabetes, the body's cells that make insulin (called beta cells) are destroyed, so no insulin is made. In type 1A diabetes, this happens because the immune system attacks these cells. Type 1B (idiopathic diabetes) happens when beta cells are lost, but the cause is unknown. Type 2 diabetes is usually linked to family history, lifestyle, and environment. Gestational diabetes happens during pregnancy when the body makes less insulin, which raises blood sugar levels[1].Type 1 diabetes (T1DM) happens when the beta cells in the pancreas (found in the islets of Langerhans) are destroyed. These cells make insulin, so their loss causes a complete lack of insulin in the body. Type 1A diabetes, also called insulin-dependent diabetes, is caused by the immune system attacking and destroying the beta cells. The speed of destruction can be different for different people. Type 1B diabetes, or idiopathic diabetes, is when beta cells are lost but there is no clear immune system attack or other known reason for insulin deficiency[2].

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

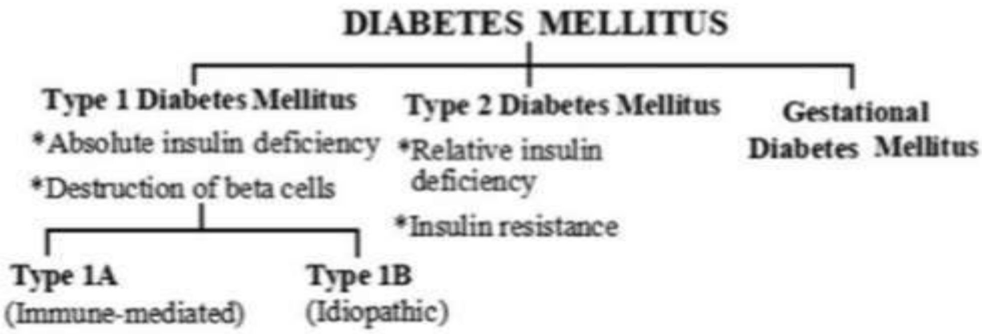

Fig. 1 – Classification of diabetes mellitus.

Type 2 diabetes (T2DM), which makes up about 90–95% of all diabetes cases, happens when the body does not use insulin properly (insulin resistance) and also does not make enough insulin. This type is linked to both genetics and lifestyle factors, like poor diet or lack of exercise. Obesity is common in people with type 2 diabetes, and many do not know they have it for years[3]. The International Diabetes Federation reported that about 12% of global healthcare spending was used for diabetes in 2015, which was around USD 673 billion. This cost is expected to rise to USD 802 billion by 2040.The serious complications of diabetes, which can cause early death and put a heavy financial burden on healthcare systems, highlight the need for better drug delivery systems. These systems can help improve blood sugar monitoring and treatment for diabetes, making it easier to manage this growing problem. People with type 1 diabetes need a constant supply of insulin, usually taken as daily injections. Type 2 diabetes is mainly treated with medicines that lower blood sugar, with metformin being the most common. Some patients with type 2 diabetes also need insulin injections[4].

1. Transdermal Drug Delivery Systems

The skin is the largest organ in our body and gets about one-third of the total blood supply. Until the late 20th century, it was not used as a way to give medicines for the whole body. In the last ten years, transdermal drug delivery (using patches on the skin) has become more popular because it has many benefits compared to taking medicines by mouth. The global market for these systems is expected to reach about $95.57 billion by 2025. When medicines are taken by mouth or injection, the amount of drug in the blood can go up and down too much. This can cause overdosing or make it hard to keep the right level of medicine in the blood. Transdermal systems solve this problem because the drug goes directly into the blood through the skin, avoiding the liver and stomach, which can change how the drug works. This improves the amount of drug that reaches the blood, lowers the chance of side effects, and makes it easier for patients to follow their treatment. Skin patches are also simple to use and release medicine slowly over time, so they don't need to be used as often[5]. Transdermal drug delivery systems are designed to deliver an exact dose of medicine through the skin directly into the bloodstream. For these systems to work effectively, the drug must penetrate the skin and reach the target site quickly. Among the available methods, the transdermal route is considered one of the best ways to deliver insulin because it allows the drug to cross the skin.

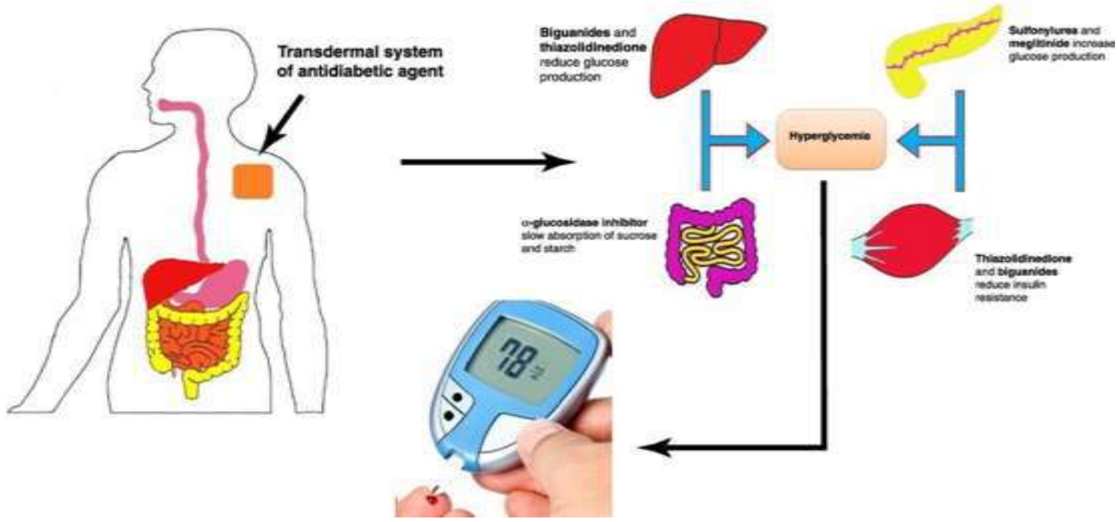

Fig 2: Transdermal system of antidiabetic agent

1. Fundamentals of Skin Permeation.

Until the last century, skin was considered impermeable except for gases. However, modern studies have shown that it can allow the passage of lipid-soluble drugs, including electrolytes. because only a few drugs have proven effective delivered through the skin typically cardiac drugs such as nitroglycerin and hormones such as estrogen[7].

A. Stratum Carenum as Skin Permeation Barrier [8]

On average, human skin has about 40–70 hair follicles and 200–250 sweat ducts per square centimeter. Although water-soluble substances can pass more quickly through these ducts, their overall contribution to skin permeation is minimal. As a result, most neutral molecules cross the stratum carenum through passive diffusion. This means the stratum carenum functions as a passive, yet active, diffusion barrier.

Series of steps in sequence:

- Sorption of a penetrant molecule on surface layer of stratum carenum.
- Diffusion through it and viable epidermis.

The molecule is taken up into the microcirculation for systemic distribution (Fig. 4).

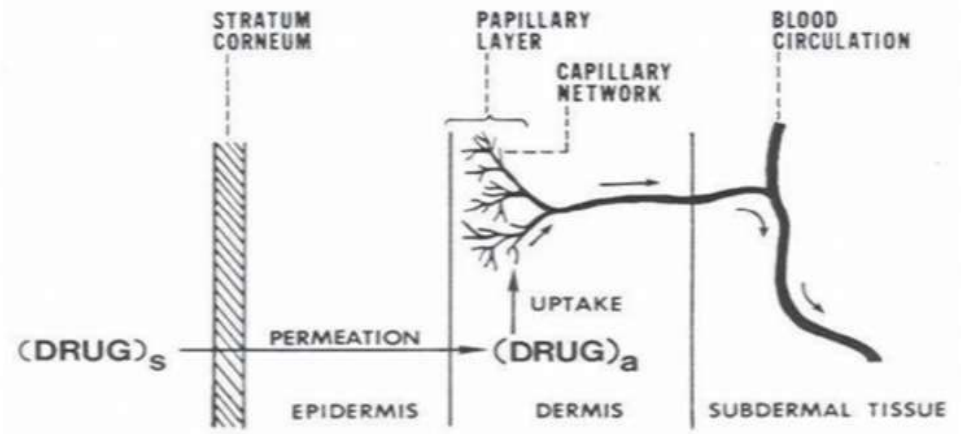

Fig 4: A multilayer skin model showing sequence of transdermal permeation of drug for systemic delivery.

B. Permeation pathways [9]: Percutaneous absorption occurs when substances passively diffuse through the skin. Molecules can enter intact skin by two main pathways: the appendageal route and the epidermal route. Percutaneous absorption refers to the process by which drugs or other substances penetrate the skin and reach the systemic circulation. This usually happens through passive diffusion, meaning it does not require energy.

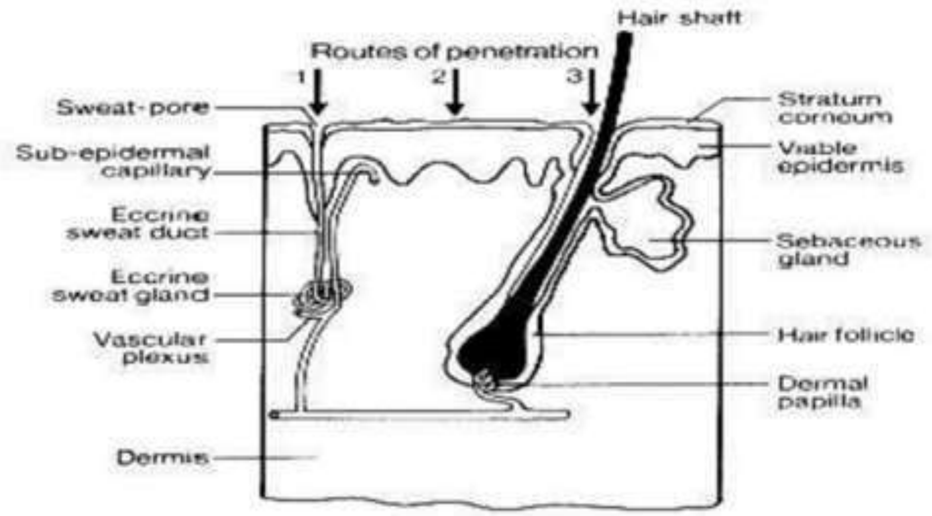

Fig 5: Routes for drug permeation

1. Appendageal route [10]

The appendageal route is a special pathway through which substances can pass into the body using the tiny openings of sweat glands, hair follicles, and their connected oil (sebaceous) glands (shown as numbers 1 and 3 in Fig. 5). This pathway is different from the main skin barrier because it completely avoids the stratum corneum, which is the thick outer protective layer of the skin. For this reason, it is often called a "shunt route," meaning it works like a shortcut that allows certain molecules to enter the deeper layers of the skin more easily. Even though this route can make it easier for some substances—especially small water-soluble molecules or drugs in liquid form—to pass through the skin, it is still considered to play only a small role in overall absorption. This is because the openings of sweat glands and hair follicles make up only about 0.1% of the entire surface area of the skin, which is very small compared to the total skin area. Therefore, the amount of drug or chemical that can be absorbed through this route is limited. However, this pathway may still be important for some special drug delivery methods, like when using very tiny particles (nanoparticles) or ions, because these can use the appendageal route to reach deeper layers of the skin more effectively.[11]

2. Epidermal route [12]

The epidermal route is the main pathway by which drugs and other substances pass through the skin to enter the body. It involves drug movement across the epidermis, which is the outermost layer of the skin. The epidermis has a strong protective barrier called the stratum corneum, made up of dead, flattened cells (corneocytes) surrounded by lipids (fats). For a drug to reach deeper layers, it must cross this barrier.

Importance of Epidermal Route [13]

- It is the primary route of percutaneous (through-skin) absorption for most topical and transdermal drugs.
- It acts as a selective barrier, allowing only certain molecules to pass depending on their size, solubility, and chemical nature.
- It is used in transdermal patches, ointments, creams, gels, etc.

For drugs, which mainly cross-intact horny layer, two potential micro routes exist, the transcellular (intracellular) and intercellular pathways (Fig. 6).

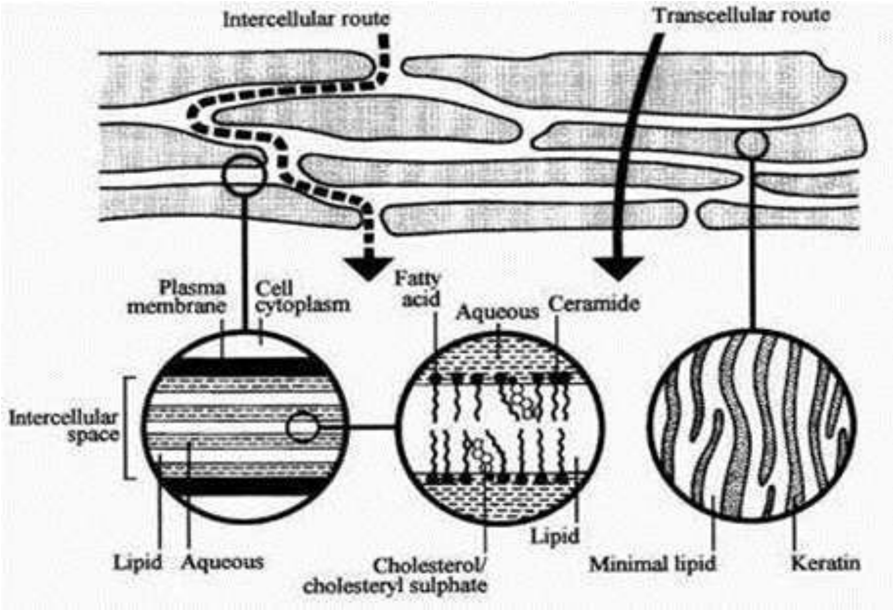

Fig 6: Epidermal routes for drug permeation

A. Ideal molecular properties for transdermal[14]: Ideal molecular properties for drug penetration are as follows:

- The partition coefficient tends to be higher when the drug's molecular weight is below 600 Daltons.
- For effective skin penetration, the drug should have good solubility in both lipids and water (log P between 1 and 3).
- The drug should preferably exist in a non-ionic form.
- An optimal partition coefficient is essential for achieving the desired therapeutic effect.
- A low melting point of the drug (below 200°C) is preferred.

C. Employment of microneedle in patch[15]

Microneedle have been widely investigated for the development of insulin patches. Various materials are used to prepare microneedle, and their dimensions such as length, diameter, and the type of excipients are carefully modified to achieve the most effective and desirable outcomes. Currently, diabetes treatment mainly relies on oral medications and insulin injections. Although microneedle-based insulin patches have shown significant potential, they are still in the research stage and not commonly used in routine therapy. Ongoing studies continue to explore their pharmacological properties, design variations, and the challenges that need to be addressed. The following research works provide valuable insights into different microneedle patch formulations.

1. Gelation and hydroxyapatite fabricated bio ceramic composite microneedle.[16]

Studied biodegradable bio ceramic composite microneedles made from gelatin and hydroxyapatite for transdermal insulin delivery. These microneedles showed good mechanical strength, biocompatibility, and low toxicity, with minimal skin damage that healed within an hour. In diabetic mice, insulin-loaded microneedles provided a prolonged hypoglycemic effect compared to subcutaneous injections due to sustained insulin release, maintaining plasma insulin levels longer and improving glucose control. Although the materials are generally safe, hydroxyapatite and gelatin showed low cytotoxicity with cell viability above 98%.

2. Double-layered, bullet-shaped microneedle with Swellable tips patch.[17]

Scientists made special double-layered, bullet-shaped microneedles with tips that can swell after entering the skin. These tips hold insulin and slowly release it over time. Unlike regular coated microneedles that release most of the insulin quickly (within 30 minutes), these swellable microneedles release insulin steadily for up to 12 hours. This helps keep blood sugar levels under control for a longer time. The patches stick well to the skin, go just under the surface, and do not cause swelling or irritation — making them a good option for diabetes treatment.

3. **Biodegradable alginate and hyaluronate polymer microneedle patch.[18]**

Researchers developed a biodegradable microneedle patch made from alginate (Alg-APBA) and hyaluronate (HA). These microneedles quickly dissolve in the skin and can bind with glucose, allowing insulin release to adjust based on glucose levels. In animal tests, more than 90% of insulin was steadily released within 6 hours, and the insulin remained active. Compared to regular injections, these patches provided similar blood sugar reduction but kept glucose levels stable for a longer time. Since alginate and hyaluronate are natural, the patch is safe, non-toxic, and biodegradable. It also prevents sudden drops in blood sugar and delivers insulin effectively through skin capillaries and lymph. However, precise design is important to maintain strength and proper skin insertion.

4. **Alginate and maltose microneedle patch.[19]**

A microneedle patch made from alginate and maltose (cross-linked with calcium) showed improved strength and durability compared to plain alginate microneedles. It released over 80% of insulin in just 8 minutes during lab tests. In animal studies, the patch lowered blood sugar more slowly but kept it stable for a longer time than regular injections, reducing the risk of hypoglycemia. Microneedles are the most widely studied method for transdermal insulin delivery because they provide sustained and controlled glucose management. They are usually made from biodegradable polymers that safely dissolve in the skin, but their safety and insertion strength must be carefully tested to ensure full drug delivery. Overall, microneedle patches show great promise as a painless and more effective alternative to subcutaneous injections, and further improvements in their design could make them even better.

CONCLUSION:

Diabetes is a long-term disease that needs regular medicine and glucose monitoring. If transdermal patches can be successfully developed, they could change how diabetes is managed. These patches can provide better drug absorption, reduce how often medicine needs to be taken compared to daily pills or multiple insulin injections, and make treatment easier — just apply a patch with a fixed release rate. They also give steady drug release, helping maintain better glucose control. Advanced patches with microneedles can even sense glucose levels and release medicine when needed, lowering the risk of hypoglycemia. Compared to insulin injections, patches can reduce stigma, needle fear, and the hassle of injecting in public.

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