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UNLOCKING THE POTENTIAL OF TRANSDERMAL DRUG DELIVERY FOR EFFECTIVE DIABETES CONTROL: A REVIEW

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Article Info

Abstract

Diabetes mellitus is a chronic condition in which the blood glucose level gets abnormally higher than the normal range. It usually occurs due to insufficient insulin production or maybe because the body is unable to utilize insulin. To treat this metabolic disorder, oral and parenteral treatment methods are utilized but these methods are quite painful, have poor patient compliance, and have a risk of infections. However, instead of injection and oral drug delivery, TDD can be preferable as it is less painful, provides better patient compliance and has a sustained drug release mechanism. Moreover, it shows higher bioavailability as it bypasses the first-pass effect. Several studies and research have already been conducted on developing and improving the TDD system for diabetes management. In this research work a comprehensive review of past studies has been presented to focus on the use of the transdermal drug delivery system (TDD) as an effective treatment method for diabetes mellitus. The aim is to highlight the transdermal drug delivery treatment and procedures that have been implemented in diabetes management.

Keywords:

Diabetes Mellitus, Transdermal Drug Delivery, Insulin, Patient Compliance, Sustained Release.

Introduction

Diabetes Mellitus is a prevailing chronic metabolic disorder indicated by the inability of the body to regulate blood sugar levels effectively[1]. It requires long-term management to prevent complications such as cardiovascular disease, kidney damage, and neuropathy. Diabetes mellitus is mainly divided into two categories: Type 1 and Type 2 diabetes.[2] based on its insulin dependency.

Diabetes Type-1, also known as insulin-dependent diabetes mellitus (IDDM) or juvenile diabetes, is an autoimmune illness in which an individual's the immune system unintentionally damages and kills the pancreatic cells that produce insulin. [3]. Type 1 diabetes is said to result from a combination of hereditary and environmental factors[4]. The immune system's destruction of the insulin-producing cells leads to an absolute insulin deficiency.

Type 2 diabetes, known as non-insulin-dependent diabetes mellitus (NIDDM)[5] or adult-onset diabetes[6], is a metabolic disorder characterized by insulin resistance, where cells become less responsive to insulin or insulin deficiency. Both genetic and lifestyle factors can be the cause of type 2 diabetes. Obesity, sedentary lifestyle, poor dietary habits, and advancing age are key risk factors[7].

Nowadays, many methods for the management of diabetes mellitus are available including oral medications and self-injectable insulin doses. However, these methods can be challenging, especially for patients receiving self-injectable doses of insulin who are at high risk of localized necrosis, microbial contamination, discomfort, and inconvenience[8].

For better patient compliance and to reduce discomfort and chances of side effects, a transdermal drug delivery system (TDD) represents a significant advancement in diabetes management and proves to be more feasible than other methods [9].

The Transdermal drug delivery system involves the administration of therapeutic agents or medicaments using sticky patches/transdermal devices that pass across the skin through diffusion and enter directly into the systemic circulation. This technique has proven to be a better alternative to various routes of administration.

Advantages of Transdermal Drug Delivery System

Only the desired amount of drug can be delivered. It is more advantageous for unconscious patients. They are easy to be self-administered [10]. The drug administered through this method bypasses the "first-pass metabolism"[11]. This technique helps in reducing the dosing frequency[12]. It is a painless and minimally invasive method and it also improves patient compliance [13].

Disadvantages of Transdermal Drug Delivery System

Drugs of smaller molecular size can be administered by this method [14].The patch can irritate the site of the application [15].This method does not support the administration of ionic drugs [16]. Large doses are difficult to administer [17]. The penetration rate of the drug across the skin depends on the site of application [18].

Limitations of Transdermal Drug Delivery System

Transdermal drug delivery is suitable for drugs with specific physicochemical properties, such as small molecular weight, lipophilicity, and moderate potency. Larger or hydrophilic drugs may have difficulty crossing the skin barrier[19].Variations in skin thickness, hydration levels, and skin conditions among individuals can lead to variable drug absorption rates, affecting the consistency of therapeutic effects[20].

Transdermal drug delivery is generally slower compared to other routes, limiting its use for drugs requiring rapid onset of action[21]. The amount of drug that can be delivered through the skin is restricted by the size of the patch and the drug's potency. High-dose medications or those with a narrow therapeutic index may not be suitable for transdermal delivery[22]. Some drugs or formulation components in the patch might become the reason for skin irritation or allergic reactions in some individuals, limiting patient compliance[23]. Over time, the drug reservoir within the patch may be depleted, decreasing drug delivery rate and potentially reducing therapeutic efficacy[24]. Proper patch adhesion to the skin is crucial for effective drug delivery. Factors like sweating, oily skin, or body hair can affect adhesion, leading to patch detachment and reduced drug delivery[25]. The placement of transdermal patches is generally restricted to hairless and relatively flat areas of the skin, limiting the convenience of patch use in certain populations[26]. Environmental factors like high temperatures and humidity levels can impact the stability of drugs within the patch, potentially reducing drug efficacy or shelf life[27]. Proper disposal of used patches containing residual drugs is essential to avoid accidental exposure and potential environmental pollution.

Composition of Transdermal Patch:

A transdermal patch may consist of components like a polymer matrix, release liner, drug, permeation enhancer, adhesive, baking films[14] as depicted in **Figure 1**. The main membrane of a transdermal patch is made of a polymer matrix which regulates the dosage of drugs released from the patch [29]. Usually, the drug reservoir is covalently bonded to two polymer layers face to face as a follicle [30]. The polymers predominantly used in transdermal patch include Natural Polymer, Synthetic elastomers and Synthetic polymer [31].Release liners are vital for upholding the patch's safety, stability, and affectivity. It protects the system and must be taken off before a patch is applied to the skin.[32]. The drug is present in direct contact with the release liner. The drug to be administered via transdermal patch should have both lipophilic and hydrophilic properties, should be of low molecular weight, the drug should be non-irritating and should have a low melting point[33]. Permeation enhancers are compounds, added in a transdermal patch for the effective permeability of the drug across the skin [34] by improving the partitioning of the drug into stratum corneum. These permeation enhancers should be non-toxic, non-irritant must have good solvent properties, and must be compatible with drugs and other excipients[35].Adhesives are one of the most crucial components of transdermal patches that maintain the contact between the patch and the skin and keep it intact with the skin and confirm the efficient delivery of drugs [36]. Baking films provide support to the drug and protect it from the outer environment and prevents the drug from leaving the dosage form. The baking films should be impermeable to the excipients and the drug and should have sufficient flexibility, elasticity, and tensile strength [37].

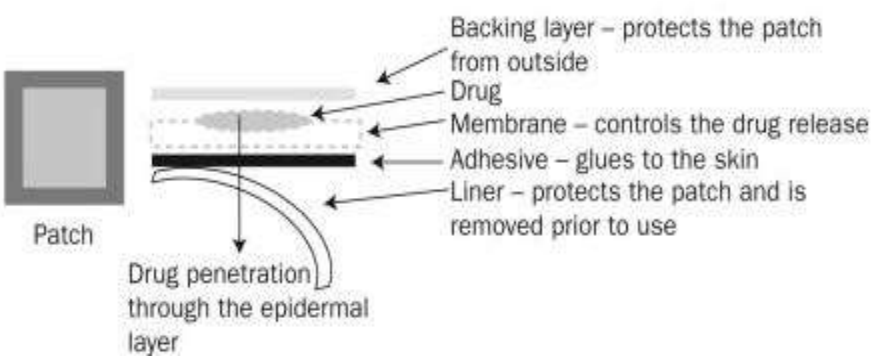

Figure 1: Layers of transdermal patch.

Mechanism of action of TDDs:

The transdermal mechanism of action involves several key steps that enable medication absorption via the epidermis and subsequent systemic distribution. As the skin is the largest organ of the human body, hence it is also the most important means of drug administration and also serves as the barrier to the transdermal absorption of various drugs[38]. There are three primary layers of human skin: the epidermis, dermis, and hypodermis. [39]. These three layers can be quite important to enhance knowledge of the transdermal mechanism of action.as shown in the **Figure 2**. The epidermis is composed of predominantly stratified keratinized squamous epithelium. The epidermis helps in protecting the body from external influences. The epidermis comprises the stratum corneum (the greatest permeability barrier in TDDs) and viable epidermis. The connective tissue, blood vessels, nerves, and appendages like sweat glands and hair follicles make up the dermis, which is located beneath the epidermis. The innermost layer, the hypodermis, is primarily made up of adipocytes, or fat cells, which act as cushions and insulation.

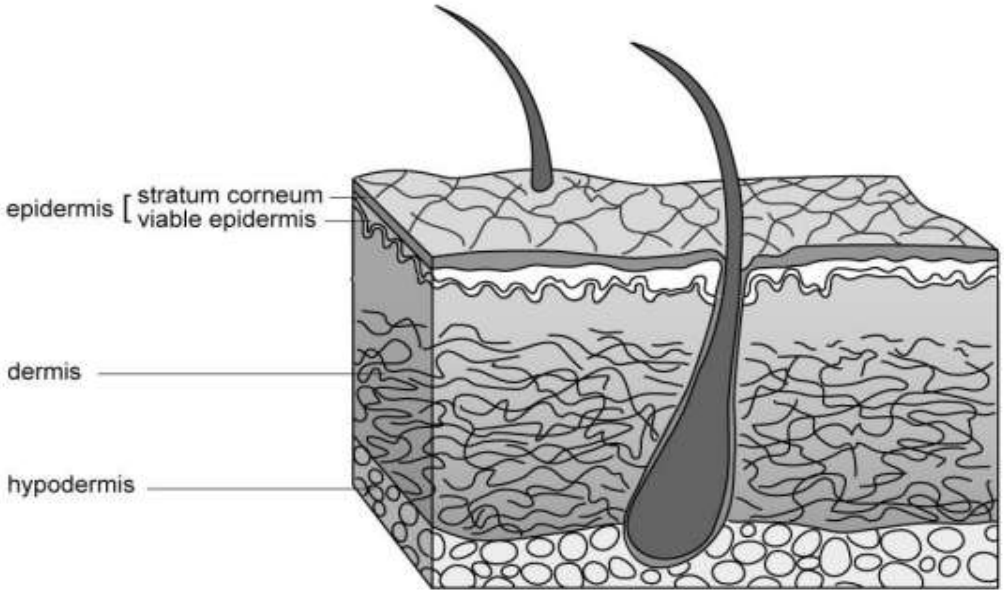

Figure 2: Anatomy of skin.

Drug Penetration and Absorption:

The stratum corneum, the outermost layer of the epidermis, acts as the primary barrier to drug absorption. To penetrate this layer, drugs must possess certain physicochemical properties, such as appropriate lipophilicity and molecular weight. Lipophilic drugs with low molecular weight generally penetrate the stratum corneum more effectively. Drug molecules can penetrate the stratum corneum through two main pathways. In the transcellular route, drug molecules pass directly through the corneocytes called the transcellular route. This pathway requires drugs to be small and lipophilic to cross both the lipid-rich intercellular spaces and the corneocyte itself. In the intercellular route, drug molecules traverse the intercellular spaces between the corneocytes. This pathway relies on the diffusion of drugs through the hydrophilic channels formed by the gaps between the corneocytes represented in **Figure 3.**

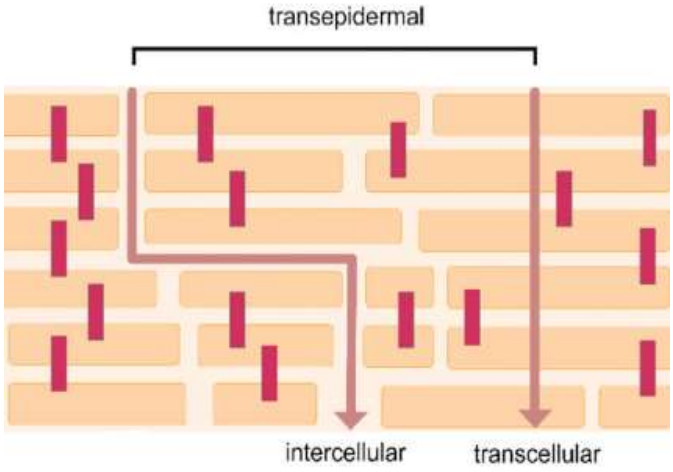

Figure 3: Diagrammatic representation of trans-epidermal routes.

Trans-appendageal penetration:

Other than trans-epidermal penetration (intercellular and transcellular penetration) drugs can also penetrate through hair follicles (trans-follicular penetration) and sweat glands (trans-glandular penetration), this route is known as the trans-appendageal route of penetration. But in contrast to trans-epidermal penetration, trans-appendageal penetration has a smaller absorption area **Figure 4** .

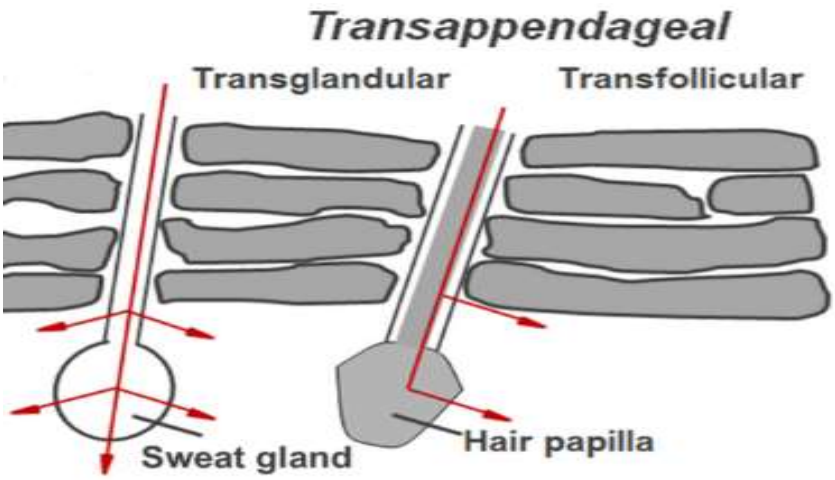

Figure 4: Schematic representation of trans-appendageal penetration.

This drug diffusion through the epidermal layers is governed by factors like the Lipophilicity of drugs, which tend to diffuse more readily through the stratum corneum's lipid-rich environment and the epidermis's intercellular spaces. It size, as a smaller drug molecules diffuse more easily through the skin compared to larger molecules. Neutral or lipophilic drugs generally diffuse more efficiently through the skin than highly charged or hydrophilic molecules. Once drug molecules have successfully crossed the epidermis, they enter the dermis, which contains blood vessels and capillaries. In the dermis, drugs can be absorbed into the systemic circulation through two main mechanisms. Drug molecules diffuse from the dermis into the capillaries by following concentration gradients as shown in **Figure 5**. This passive diffusion process is driven by the difference in drug concentrations between the dermis and the blood vessels. Whereas in active Transport drugs employ active transport mechanisms to facilitate their

absorption into the bloodstream. These mechanisms involve specific carrier proteins or transporters present in the endothelial cells lining the blood vessels.

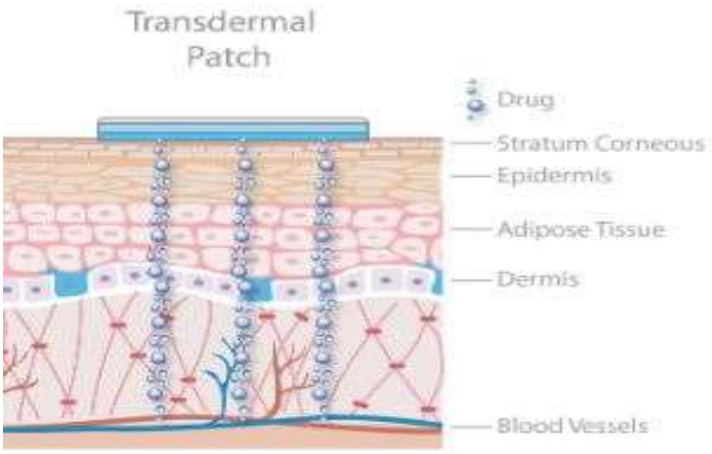

Figure 5: Mechanistic analysis of drug penetration

Table 1: Common Drugs Administered via Transdermal Drug Delivery System:

Drug Name	Implications	Common Applications	References
Nitroglycerin	Angina pectoris	Chest pain due to heart disease	[40]
Fentanyl	Pain management	Chronic pain relief	[41]
Estradiol	Hormone replacement therapy	Menopausal symptoms, osteoporosis	[42]
Nicotine	Smoking cessation	Nicotine addiction treatment	[43]
Scopolamine	Motion sickness	Prevention and treatment of motion sickness	[44]
Rivastigmine	Alzheimer's disease	Cognitive improvement in Alzheimer's disease	[45]
Lidocaine	Local anesthesia	Pain relief for minor surgical procedures	[46]
Oxybutynin	Overactive bladder	Urinary incontinence treatment	[47]

Rotigotine	Parkinson's disease	Management of Parkinson's disease	[48]

Table 2: TDDS in Diabetes Mellitus

Drug Name	Effect	Implications	References
Insulin	Glycemic control	Diabetes mellitus type 1 and type 2	[49]
Exenatide	Glucose regulation	Type 2 diabetes mellitus	[50]
Pramlintide	Blood sugar control	Diabetes mellitus type 1 and type 2	[51]
Metformin	Glucose management	Type 2 diabetes mellitus	[52]
Rosiglitazone	Insulin sensitivity	Type 2 diabetes mellitus	[53]
Saxagliptin	Incretin-based therapy	Type 2 diabetes mellitus	[54]
Canagliflozin	Sodium-glucose co-transporter 2 inhibitor	Type 2 diabetes mellitus	[55]
Glimepiride	Blood sugar lowering	Type 2 diabetes mellitus	[56]
Liraglutide	Glucose control	Type 2 diabetes mellitus	[57]
Insulin Glargine	Long-acting insulin analog	Both type 1 and type 2 diabetes mellitus	[58]

The above table comprises different diabetic drugs that are formulated as transdermal patches to facilitate drug delivery. Exenatide is a drug used to improve glucose regulation in the treatment of diabetes type 2. The transdermal patch of exenatide proves to be an excellent and painless alternative to the subcutaneous injections [59]. Transdermal administration of Metformin is safer, more feasible, and economical and provides continuous delivery of drug across the skin[60]. Rosiglitazone, an antidiabetic agent, improves insulin sensitivity in Type 2 diabetes and is usually administered orally twice a day but Transdermal delivery can improve its bioavailability and can also reduce the dosing frequency[61]. The transdermal patch of Saxagliptin is useful for the management of blood sugar for a longer duration in the treatment of diabetes type 2. This formulation helps in avoiding the first pass effect and overdosing can also be reduced by this method[62].

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