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A Review on Transdermal Patches

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Abstract:

Transdermal drug delivery systems (TDDS) offer a promising approach for the controlled and sustained release of drugs through the skin, providing several advantages such as improved bioavailability, avoidance of first-pass metabolism, and enhanced patient compliance. This review focuses on the formulation and evaluation of transdermal patches containing Nateglinide, a short-acting insulin secretagogue used in the management of type 2 diabetes mellitus. Nateglinide exhibits low oral bioavailability and a short half-life, necessitating frequent dosing; thus, transdermal administration can help overcome these limitations. Various formulation methods—including solvent casting, film deposition, and matrix dispersion techniques—are discussed, with emphasis on the selection of suitable polymers (such as HPMC, Eudragit RL/RS, PVP, and ethyl cellulose) and plasticizers (like dibutyl phthalate and PEG 400) to achieve optimal patch flexibility and controlled drug release. Permeation enhancers such as oleic acid, propylene glycol, and DMSO play a vital role in enhancing drug flux through the stratum corneum. Evaluation parameters—thickness, tensile strength, folding endurance, moisture content, drug content uniformity, in vitro drug release, and ex vivo skin permeation studies—are critically reviewed. The transdermal delivery of Nateglinide offers a novel strategy for sustained glycemic control, reduced dosing frequency, and improved therapeutic efficacy in diabetes management.

Keywords: Transdermal drug delivery system (TDDS); Nateglinide; Type 2 diabetes mellitus; Controlled release; Solvent casting method; Polymer matrix.

Introduction

Transdermal drug delivery systems (TDDS) are an advanced method of drug administration that allows drugs to be absorbed through the skin and directly enter the systemic circulation. This method offers several advantages over conventional oral and injectable routes, including avoiding first-pass metabolism, reducing dosing frequency, and enhancing patient compliance. TDDS provides controlled and sustained drug release, which helps in maintaining consistent plasma drug levels,

reducing side effects, and improving therapeutic efficacy. A transdermal patch is a medicated adhesive patch that is applied to the skin to deliver a particular amount of medicine into the circulation. The patch provides a controlled release of medication into the patient, usually through a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive, which is an advantage of transdermal drug delivery over other types of medication delivery (such as oral, topical, intravenous, or intramuscular). The fundamental disadvantage of transdermal delivery methods is that the skin is a highly efficient barrier; hence, only drugs with molecules tiny enough to permeate the skin may be supplied this way. The US Food and Drug Administration authorised the first commercially accessible prescription patch in December 1979. For motion sickness, these patches delivered scopolamine.

TDD is a painless method of systemic drug delivery in which a drug formulation is applied to healthy, undamaged skin.

The medication passes through the stratum corneum and then deeper layers of epidermis and dermis without accumulating in the dermal layer. When medicine reaches the dermal layer, it is available for systemic absorption due to dermal microcirculation. TDD has several advantages over more typical medicine administration systems. It may provide a non-invasive alternative to parenteral techniques, eliminating issues such as needle phobia. Because of the large surface area of skin and ease of access, there are various options for transdermal absorption placement on the skin.[1]

Furthermore, the pharmacokinetic profiles of medications have fewer peaks and are more constant, lowering the probability of adverse side effects. It is effective for patients who are sleepy, vomiting, or rely on self-administration, and the reduction in dosage frequency can promote patient compliance. TDD increases bioavailability by preventing pre-systemic metabolism. Concerning the use of the skin as a novel site for vaccination approaches, it is well known that this organ is teeming with dendritic cells in both the epidermal and dermal layers, which are critical for immune responses and make TDD an ideal vaccination route for therapeutic proteins and peptides. Because of the need for a low-cost, non-invasive technique of immunisation, particularly in poor countries, much research has been conducted on the development of simple, needle-free methods such as TDD for vaccination purposes.

It was thought that the skin served as a solid barrier. Munitions workers in World War II had fewer angina attacks when they used nitroglycerin around the turn of the century. This has called into question the common understanding that the skin acts as a full barrier of protection, and it has spurred a flurry of study into the possibility of transdermal medication delivery for systemic treatment.[2]

Transdermally controlled drug delivery systems (TDDS) have recently been created with the objective of delivering systemic therapy by transdermally controlled drug administration. Scopolamine-releasing TDD systems were successfully created in 1981 (Ciba, Transderm- Scop system) for 72-hour motion sickness and nausea prevention or therapy.

Following that, several nitroglycerin-releasing TDD systems for once-daily angina pectoris treatment, clonidine-releasing TDD systems for weekly hypertension therapy, and estradiol-releasing TDD systems for twice-daily use were commercially successful. Because of the inherent benefits of administration through this route, new medications are being

created utilising transdermal systems in addition to those that are already on the market. For smoking cessation therapy, buspar, an anti-anxiety medication, and nicotine and mecamylmine are being developed for TDDS and are now completing phase III clinical studies.[3]

Types

Sample transdermal patches. On left is a 'reservoir' type, on the right a 'Single-layer Drug-in- Adhesive' version. Both contain exactly the same active ingredient with identical release rates.[4,5]

There are five main types of transdermal patches.

A. Single-layer Drug-in-Adhesive

This system's sticky layer also contains the medication. The adhesive layer of this sort of patch not only helps to glue the numerous layers together, as well as the entire system to the skin, but it is also responsible for medication release.

B. Multi-layer Drug-in-Adhesive

The multi-layer drug-in-adhesive patch is similar to the single-layer system; however, the multi-layer system differs in that additional layer of drug-in-adhesive is added, generally separated by a membrane (but not in all cases).

This patch has a temporary liner layer as well as a permanent backing. The drug release from this is determined by membrane permeability and drug molecule diffusion.

C. Reservoir

The reservoir transdermal system, unlike the single-layer and multi-layer drug-in-adhesive systems, has a distinct drug layer. The drug layer is a liquid compartment divided by the adhesive layer that contains a drug solution or suspension. The drug reservoir is completely enclosed in a shallow compartment constructed of a drug-impermeable metallic plastic laminate.

D. Matrix

The matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer, partially overlaying it. Also known as a monolithic device.

E. Vapour Patch

In a vapour patch, the adhesive layer not only serves to adhere the various layers together but also to release vapour. Vapour patches release essential oils for up to 6 hours and are mainly used for decongestion. Other vapour patches on the market improve quality of sleep or aid in smoking cessation.

Innovation in Transdermal drug delivery systems [6,7]

To give a method of rate control over the release and transdermal penetration of medicines, a number of strategies have been successfully established. To be accurate, the design of TDDS incorporates two concepts: system controlled device and skin controlled device (monolith type).

Skin controlled device: (Monolith or Matrix System)

The skin will control the rate at which the drug diffuses into the body. The vast majority of skin-controlled devices are monolithic, with a drug-containing matrix layer sandwiched between the frontal and backing layers. The polymer matrix controls the release rate, which is frequently greater than the penetration rate through the skin.

System controlled device: (Reservoir or Membrane System)

The majority of the control over the rate of medication entry into the body is provided by the transdermal system. A rate-controlling membrane, a reservoir

containing the medication (often in liquid or generic form), a sticky layer, and protective layers are other functional elements of system-controlled devices. When the required rate of drug delivery is much slower than that through the skin, this sort of device is advantageous.

Polymer membrane permeation – controlled systems

The drug reservoir is enclosed in a compartment consisting of a rate-regulating polymeric membrane and a drug-impermeable backing layer in this approach. In the drug reservoir compartment, the drug particles are either suspended in an unleachable, viscous liquid media or spread in a solid polymer matrix. A small coating of a drug-compatible adhesive polymer, such as silicone or polyacrylate glue, is applied to the polymeric membrane's exterior to provide a close bond between the device and the skin surface.

Matrix diffusion - controlled systems

To provide the drug reservoir in these types of devices, the hydrophilic or lipophilic polymer used to create the medicated polymer is then moulded into a medicated disc with a specific surface area and thickness. The base plate is then bonded to a drug-impermeable backing before being adhered to the medicated disc. Instead of an adhesive overlay, the majority of these systems include a peripheral adhesive ring.

Need for Study

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels due to impaired insulin secretion or action. Among various antidiabetic agents, Nateglinide, a rapid-acting insulin secretagogue, is commonly used to manage postprandial hyperglycemia in Type 2 Diabetes Mellitus (T2DM). However, its short half-life (~1.5 hours) and extensive first-pass metabolism significantly reduce its bioavailability and require frequent dosing, leading to poor patient adherence and suboptimal glycemic control. To overcome these limitations, there is a growing interest in Transdermal Drug Delivery Systems (TDDS) as an alternative to conventional oral therapy. This study is essential for the following reasons:

Overcoming Limitations of Oral Nateglinide Therapy

- Oral administration results in low bioavailability (~23%) due to extensive first-pass metabolism.
- Frequent dosing (before each meal) affects patient adherence.
- Potential gastrointestinal side effects (nausea, diarrhea) impact patient comfort.
- Fluctuations in plasma drug concentration can lead to inadequate glycemic control.

Advantages of Transdermal Drug Delivery

- Bypasses first-pass metabolism, enhancing systemic bioavailability.
- Provides sustained drug release, ensuring stable plasma drug levels and better glycemic control.
- Reduces dosing frequency, improving patient compliance and convenience.
- Minimizes gastrointestinal side effects, making it a more patient-friendly alternative.

Potential Clinical and Therapeutic Impact

- Development of a patient-friendly, non-invasive alternative to oral Nateglinide therapy.
- Reduction in dosing frequency and side effects, leading to better patient

adherence and improved therapeutic outcomes.

- Contribution to personalized diabetes management, allowing for controlled and sustained drug release.

Methods for Preparation of Transdermal Patches [8-13]

Transdermal patches are designed to deliver drugs across the skin at a controlled rate for systemic therapeutic effects. Several formulation methods are employed depending on the drug properties, polymer type, and desired release profile.

The major preparation methods include:

A. Solvent Casting Method

Principle:

A polymer is dissolved in a suitable solvent, drug and excipients are added, and the solution is cast into a mold. Solvent evaporation yields a thin drug-loaded film (patch).

Steps:

1. Dissolve polymer (e.g., HPMC, PVA, Eudragit) in an organic or aqueous solvent.
2. Add plasticizers (PEG 400, glycerin) to improve flexibility.
3. Dissolve or disperse the drug in the polymer solution.
4. Pour the uniform mixture into a casting plate or Petri dish.
5. Allow solvent evaporation under controlled conditions.
6. Peel and cut patches to the required size.

Advantages:

- Simple and widely used
- Suitable for heat-sensitive drugs

B. Mercury Substrate Method

Principle:

The polymeric mixture is cast on a surface of mercury to obtain an even, smooth patch.

Steps:

Same as solvent casting, but the casting is done on mercury.

Advantages:

- Produces uniform smooth films
- Useful for hydrophobic drug systems

C. Matrix Dispersion Method

Principle:

Drug is dispersed into a polymer matrix; patches are formed by spreading the mixture.

Steps:

1. Dissolve polymer in solvent.
2. Disperse drug uniformly in the polymer solution.
3. Add plasticizer and mix thoroughly.
4. Spread the dispersion on a backing membrane.
5. Dry and laminate with release liner.

Advantages:

- Works for both lipophilic and hydrophilic drugs
- Provides sustained release

D. Direct Milling / Melt Extrusion Method

Principle:

Drug and polymer are melted or milled together and cast into films without solvents.

Steps:

1. Mix drug with polymers (e.g., ethyl cellulose, EVA).
2. Melt or mill to create uniform distribution.

3. Compress or roll into films using hot-melt extruder.
4. Cut patches of required dimensions.

Advantages:

- Solvent-free
- Good for hydrophobic drugs

E. Adhesive Dispersion Method (Drug-in-Adhesive Type)

Principle:

Drug is dissolved or dispersed in an adhesive and coated onto a backing layer.

Steps:

1. Mix drug with pressure-sensitive adhesive (PSA) such as silicone, polyacrylate, or polyisobutylene.
2. Coat the mixture onto a backing membrane.
3. Dry the adhesive layer to remove solvents.
4. Apply release liner.

Advantages:

- Simple
- Produces thin and patient-friendly patches
- Useful for drugs requiring rapid onset

F. Microreservoir Method

Principle: A biphasic system is formed by dispersing drug microspheres or microreservoirs in a polymer adhesive.

Steps:

1. Form drug–polymer microspheres by dispersion.
2. Disperse these microspheres into adhesive polymer solution.
3. Coat mixture onto backing membrane.
4. Dry and laminate with release liner.

Advantages:

- Suitable for drugs needing controlled release
- Reduces burst effect

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