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A Review on Transdermal drug delivery systems (TDDS)

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Abstract:

Transdermal drug delivery systems (TDDS) have gained considerable importance as an alternative route for systemic drug administration, offering advantages such as sustained release, improved bioavailability, and avoidance of first-pass metabolism. This review focuses on the formulation and evaluation of transdermal patches containing Repaglinide and Metformin—two antidiabetic agents with complementary mechanisms of action for the effective management of type 2 diabetes mellitus. Repaglinide, a short-acting insulin secretagogue, and Metformin, an insulin sensitizer, together provide synergistic glycemic control when delivered through the transdermal route. Various formulation techniques such as solvent evaporation, film casting, and matrix dispersion methods are discussed, emphasizing the selection of suitable polymers (e.g., HPMC, PVP, Eudragit, and ethyl cellulose), plasticizers, and permeation enhancers (such as oleic acid, propylene glycol, or DMSO) to optimize drug release and skin permeation. Evaluation parameters including thickness, weight variation, folding endurance, drug content uniformity, moisture uptake, tensile strength, in vitro drug release, and ex vivo permeation studies are reviewed comprehensively. The transdermal patch formulation of Repaglinide and Metformin offers a promising approach for achieving controlled and sustained plasma drug levels, improving therapeutic efficacy, reducing dosing frequency, and enhancing patient compliance in long-term diabetic therapy.

Keywords: Transdermal drug delivery system (TDDS); Repaglinide; Metformin; Type 2 diabetes mellitus; Controlled release.

Introduction

Transdermal drug delivery systems (TDDS) are an advanced method of drug administration that enables medications to be absorbed through the skin and directly enter systemic circulation. This approach offers several advantages over conventional oral and injectable routes, such as bypassing first-pass metabolism, reducing dosing frequency, and improving patient adherence. TDDS ensures controlled and sustained drug release, helping maintain stable plasma drug levels, minimizing side effects, and

enhancing therapeutic efficacy. A transdermal patch is a medicated adhesive patch applied to the skin to deliver a specific dose of medication into the bloodstream. It allows for controlled drug release, either through a porous membrane covering a medication reservoir or by utilizing body heat to melt thin layers of the drug embedded in the adhesive. This controlled release mechanism provides a significant advantage over other administration methods, including oral, topical, intravenous, and intramuscular routes. However, a key limitation of transdermal drug delivery is that the skin acts as an effective barrier, restricting the passage of only small-molecule drugs. The first commercially available prescription patch, approved by the US Food and Drug Administration in December 1979, delivered scopolamine for motion sickness.

Transdermal drug delivery is a painless method of systemic drug administration, where a drug formulation is applied to intact, healthy skin. The medication penetrates the stratum corneum and moves through deeper layers of the epidermis and dermis without accumulating in the dermal layer. Once the drug reaches the dermis, it becomes available for systemic absorption via dermal microcirculation.

Compared to traditional drug administration methods, transdermal delivery offers several advantages, including a non-invasive alternative to parenteral routes, eliminating concerns such as needle phobia. Additionally, the skin's large surface area and accessibility provide multiple options for absorption site selection.[1]

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.[2-3]

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, with a rate-controlling membrane made of a polymer similar to vinyl acetate on one surface. The backing layer also supports this patch. The rate of release in this system is zero order.

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 [4]

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.[5]

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.

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 Transdermal Patches in Diabetes Management [8]

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels, resulting from insufficient insulin production or insulin resistance. Effective management of diabetes requires tight glycemic control, often necessitating frequent dosing of antidiabetic medications. However, conventional oral formulations of antidiabetic drugs may pose challenges such as poor bioavailability, gastrointestinal side effects, and the need for multiple daily doses.

Transdermal patches offer a promising alternative by providing:

- Non-invasive drug administration, improving patient compliance.
- Sustained drug release, ensuring prolonged therapeutic action.
- Bypassing of gastrointestinal degradation and hepatic first-pass metabolism, leading to enhanced drug bioavailability.

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, Repaglinide and Metformin, 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:

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.
- • Non-invasive and painless, increasing acceptance compared to injectable formulations.

Need for an Optimized Transdermal Patch

- There is limited research on the feasibility for transdermal delivery.
- The selection of appropriate polymers and penetration enhancers is critical for efficient drug release and skin permeation.
- Optimization of physicochemical properties (mechanical strength, adhesion, moisture content) is necessary for patient usability.
- In-vitro and in-vivo studies are needed to confirm the efficacy and safety of transdermal patches.
- Potential Clinical and Therapeutic Impact
- Development of a patient-friendly, non-invasive alternative to oral Repaglinide and Metformin therapy.
- Reduction in dosing frequency and side effects, leading to better patient adherence and improved therapeutic outcomes.

Methods for Preparation of Transdermal Patches [9-12]

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:

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

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

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

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
- High mechanical strength

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

Micro reservoir 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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