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Recent Advances in Transdermal Patch Technology: Design, Mechanism, and Evaluation of Innovative Delivery Systems in Dermatology

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Abstract

Fungal infection, psoriasis, and localized pain are commonly encountered skin disease processes by dermatologists, which could benefit from advanced drug delivery systems. Currently suggested dermatological applications include topical preparations and/or oral medication. Both topical and oral preparations have been challenged by limited drug delivery in relation to skin penetration, patient compliance, systemic side effects, etc. Transdermal drug delivery systems (TDDS) are a new drug delivery method that provides prolonged delivery, increased bioavailability and compliance. Transdermal patches are a TDDS that avoids the gastrointestinal and hepatic first-pass, with the main advantage being controlled delivery and a non-invasive route of administration. Herein, we review the advances in TDDS including proposed formulation strategies, mechanism(s) of permeation, and evaluation strategies- both physicochemical and in vivo. Updates are provided on alternative TDDS including nanocarrier systems, microneedles, and smart patches. This review aims to provide a comprehensive overview of formulation vehicles, physicochemical and in vivo assessment strategies and methods, as well and regulatory strategies to inform prospective research.

Abbreviations

TDDS- Transdermal Drug Delivery System FDA- Food and Drug Administration
ICH- International Council of Harmonisation of technical requirement for pharmaceutical for human use. NCLs- Nanostructured Lipid Carriers
EMA-European Medicines Agency pH- Potential of Hydrogen
MNs- Microneedles

INTRODUCTION

1. Skin

The skin thus seems as the most likely route for drug administration into human body. In recent decades, attention has been given to transdermal drug delivery systems (TDDS). They can erase many limitations associated with oral administration and hypodermic injection matters Among TDDS [1], transdermal patches have been considered particularly useful. They can administer drugs in a controlled and continuous way, exaltate patient compliance and reduce side effects [2]. Transdermal patches are used to deliver therapeutic agents through the skin into the systemic circulation, and are less subject to first-pass metabolism, also providing the potential for sustained drug delivery over time. The following review article is an in-depth overview of transdermal drug delivery systems, their design, types and evaluation techniques, manufacturing methods, and an update on the novel developments in the area along with a focus on the recent Luliconazole loaded patches for antifungal therapy [3].

1.1 Structure and Function of the Skin

As the body's largest organ, the skin is an essential barrier that regulates absorption and penetration of substances and protects underlying tissues from external insults. A profound understanding of the unique organization of the skin is necessary to enable the efficacious design of transdermal drug delivery systems. The skin is made of three primary layers:

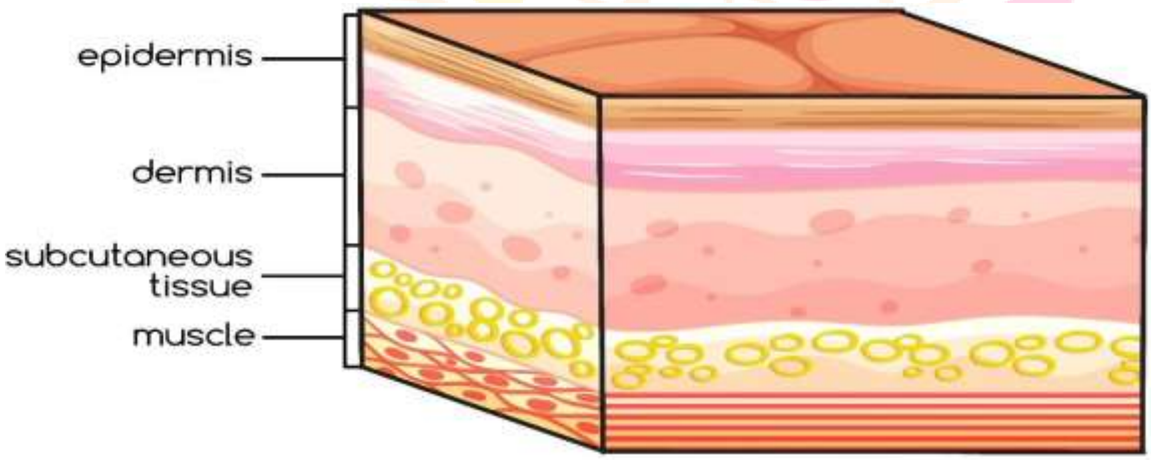

Figure 1: Structure of human skin

1. **Epidermis:** The outer layer, mainly formed of keratinocytes and constitute the primary barrier against the external agents. The most superficial sublayer, stratum corneum, serves as the principal permeability barrier [4].

2. **Dermis:** The middle layer, filled with connective tissue, blood vessels, nerve endings, hair follicles, and glands. It helps to provide structure and nutrition to the epidermis.

3. **Hypodermis (Subcutaneous tissue):** Hypodermis is a layer under the skin, which consists of adipose tissue and serves in protection and energy storage. The skin acts as a strong defence against absorption of drugs and chemicals, due to its outermost layer, the stratum corneum. It's nice to know this when designing efficient transdermal drug delivery systems that can overcome such barriers and gets the therapeutic agents to their target locations [5].

1.2 Functions of the Skin

- Protect From UV Radiation, Pathogens, and Mechanical Stress
- Sweating and blood flow as thermoregulatory responses
- Synthesis of vitamin D
- Sensation (i.e., touch, pressure, temperature, and pain)
- Antitumor immunity and immune escape
- Tissue regeneration and wound healing [6].

2. Transdermal Drug Delivery System

Transdermal drug delivery systems are defined as a delivery of drugs via skin barrier for systemic circulation without invasion. Since they facilitate drug penetration of the stratum corneum (the outer layer of the skin) and into the blood circulation directly, thus avoiding the gastrointestinal tract and hepatic first-pass metabolism, which together limit the bioavailability and the effective release of the drug

Technologically advanced formulations to deliver APIs gradually through the skin barrier for the systemic or local therapeutic effect have been referred as TDDS [7].

2.1 Absorption Pathways: The drug molecules primarily cross the skin via three routes:

1. **Transcellular Pathway:** The drug diffuses directly through keratinocytes in the stratum corneum [8].
2. **Intercellular Pathway:** The drug navigates through the lipid-rich spaces between cells in the stratum corneum [9].
3. **Appendageal Pathway:** The drug penetrates via sweat glands and hair follicles, bypassing the dense stratum corneum [10].

2.2 Transdermal Drug Delivery Mechanisms

1. **Passive Diffusion:** The most common method in which drugs undergo diffusion across the skin layers (from high concentration to low concentration).

2. **Facilitated Transport:** This method uses either chemical enhancers or physical methods to improve skin permeability.
3. **Active transport:** Draws on outside energy to drive the drug molecules through the skin (iontophoresis, electroporation) [11].

3. Transdermal Patches

Transdermal patches are drug-laden adhesive systems intended for the administration of a set quantity of medicine to the body via the skin and into the bloodstream for a specified period of time [12].

Advantages

- Easily administered in a non-invasive and painless manner.
- Enhanced bioavailability for some medications.
- Release of drugs in a controlled and sustained manner.
- Reduced dosing frequency.
- Lower avoidance of first-pass metabolism.
- Potential for self-administration, the improved compliance of the patient [13].

Disadvantage

- On potency drugs (drugs with molecular weight < 500 Da)
- Possibility of skin sensitivity or allergy
- Absorption rates that depend on individual skin variant
- Production costs that are higher than for traditional dosage forms
- Not appropriate for medications with high blood levels [14].

Drug Absorption Process

- **Drug Release:** The drug is released from the patch reservoir or matrix
- **Penetration:** The drug penetrates across the stratum corneum, the skin's main barrier.
- **Diffusion:** The drug diffuses through viable epidermis and upper dermis
- **Absorption:** The drug is absorbed in the capillary network (dermis) and then in systemic circulation [15].

4. Method of Preparation of Transdermal patch

The various methods to prepare of patches have been compared with their respective advantages and disadvantages. The specifications of the patch, drug properties and manufacturers/preferences dictate the mode of production. The most prominent ones are solvent evaporation, hot-melt extrusion, and coacervation, which result in a high degree of control of drug release rates and patch integrity in order to enhance the therapeutic outcome. Such knowledge is vital to creating patches that will not only stick to skin but also remain stable and enable the active to deliver effectively over their lifetime [20].

4.1 Solvent Casting Method

The method used most frequently to prepare matrix type transdermal patches [21].

Process:

- Dissolving drug and polymer(s) in an appropriate solvent system.
- Adding plasticizers and other excipients as necessary.
- Casting onto backing membrane.
- Allowing solvent to evaporate in controlled conditions.
- Cutting dried film into desired sized patches.

Advantages:

- Straightforward and inexpensive
- Works with heat sensitive drugs such as Luliconazole
- Dispensing uniform drug distribution

Considerations:

- Residual solvents
- May need to optimize drying conditions

4.2 Hot-Melt Extrusion

The solvent-free method of preparation is becoming more common for transdermal patches [22].

Process:

- Mixing drug with thermoplastic polymers and other excipients.
- Heating to form a molten mass.
- Extruding molten material through a die.
- Cooling and shaping extrudates into film.
- Laminating with backing layer and cutting into desired patches.

Advantages:

- Process is solvent-free
- Can accommodate drugs that have poor solubility
- Has possibilities of continuous manufacturing

Considerations:

- Process may not accommodate heat sensitive drug
- Require specific equipment

4.3 Reservoir System Preparation

The following method may be utilized in the preparation of patches which utilize reservoir transdermal systems [32].

Process:

- Drug is prepared in a drug reservoir; this may be done by dissolving the drug in the suitable solvent or dispersing the drug in a polymeric matrix.
- The drug reservoir is encapsulated by a backing layer, which is impermeable, and another rate-controlling membrane to releas the drug.
- The adhesive layer is applied to the membrane.
- Patch is cut to desired size.

Advantages:

- High drug loading is possible.
- Drug delivery has an accurate release rate.

Disadvantages:

- Manufacturing is more complex.
- If the membrane is breached, there is the potential for dose dumping.

4.4 Electrostatic Spinning

The following novel method is utilized in the preparation of nanofiber-based patches [24].

Process:

- A polymeric drug-containing solution is prepared.
- A high voltage is applied to the solution and the voltage creates a jet of the polymer solution.
- The jet collects onto a grounded collector and forms the nanofibers.
- The nanofiber mat can then be formed into a patch.

Advantages:

- Very high surface area available for drug release.
- Very thin patches can be produced.
- Use of fiber configuration to allow for controlled release.

Disadvantages:

- Requires specialized equipment.
- Difficulties with scale up.

4.5 Micro-reservoir System

This method combines elements of matrix and reservoir systems [25].

Process:

- Disperse drug in a polymer solution to form a suspension.
- Homogenize the suspension to form microreservoirs.
- Quickly crosslink the polymer to stabilize the microreservoirs.
- Cast the mixture onto a backing layer and dry.

Advantages:

- Combines benefits of matrix and reservoir systems
- Can provide both immediate and sustained drug release

Considerations:

Process parameters must be carefully optimized. The preparation method for Drug-loaded transdermal patches is dependent on multiple factors including the dosage form: release profile, type of patch design/making, stability of drug, and manufacturer's capabilities. Each method has its own strengths and weaknesses, and most importantly, when we choose a method, we conduct a balancing act based on the above factors to provide the best possible patch (performance and manufacturability)

5. Evaluation of Transdermal Patch

5.1 Physicochemical Evaluation

This section reviews a patch's physical and chemical properties (more termed as physicochemical) to ensure uniformity between batches [26].

Physical Appearance:

- The patch (or drug-loaded patch) should be evaluated for any visible defects such as cracks, bubbles, or uneven surfaces.
- Inherent properties such as color, transparency, and flexibility should be compared to a 'control patch' (one which is structurally uniform and approved for the experiment).

Thickness:

- The patches thickness in multiple spots of the patch is made with micrometer or thickness gauge.
- The thickness should be uniform throughout to provide uniform drug release.

Weight Variation:

- Each patch is weighed individually and average weight is checked for the variability between the patches.

Folding Endurance:

- A specific point in the patch is folded over and over until the patch ruptures that point, or visible cracks are seen at that point.
- The folding endurance test allows for an estimate of flexibility and durability of the patch.

Moisture Content:

- The patch is weighed before and after desiccator dry weight.

- Moisture content is important for stability and adhesion.

Moisture Uptake:

- The patch is exposed to humid conditions, and the weight gain is measured.
- This test assesses the patch's ability to withstand humid environments.

Tensile Strength:

- This measures the maximum force required to break the patch.
- The tensile strength is calculated using a texture analyser or universal testing machine.

Drug Content Uniformity:

- Patches are dissolved in a suitable solvent, and the drug content is analysed using spectrophotometric or chromatographic methods (e.g., HPLC).
- Uniform drug content ensures consistent therapeutic effects.

5.2 Adhesive Properties

Adhesion is critical for ensuring the patch remains in contact with the skin for the intended duration.

Peel Adhesion Test:

- Measures the force required to peel the patch from a standard substrate (e.g., stainless steel plate) at a 90° or 180° angle.
- Strong adhesion without causing skin irritation is desirable.

Tack Test:

- Evaluates the initial stickiness of the adhesive by measuring the force needed to separate the patch from a probe after brief contact.

Shear Adhesion Test:

- Measures the time the patch takes to detach from a substrate under a constant shear force.

5.3 In Vitro Evaluation

These tests focus on drug release profiles and transdermal patch permeation under controlled environments.

Drug Release Study:

- Conducted using a USP dissolution apparatus or Franz diffusion cell.
- The patch is placed in a receptor medium (e.g., phosphate buffer), and the drug released over time is analyzed spectrophotometrically.

Skin Permeation Study:

- Performed using Franz diffusion cells with animal or human skin as the barrier.
- The amount of drug permeating through the skin into the receptor medium is measured over time.

Release Kinetics:

- The drug release data is fitted into mathematical models (e.g., zero-order, first-order, Higuchi, or Korsmeyer-Peppas) to determine the release mechanism.

5.4 In Vivo Evaluation

The in vivo studies validate the therapeutic effectiveness, safety and the pharmacokinetics profile of the patch in living systems.

Skin Irritation and Sensitization Test:

- The patch is applied to animal or human skin, and signs of redness, swelling, or irritation are monitored.
- It ensures biocompatibility and minimal adverse reactions.

Pharmacokinetic Studies:

- Involves the measurement of drug concentration in blood plasma over time after patch application.
- Parameters like Cmax (maximum concentration), Tmax (time to reach maximum concentration), and AUC (area under the curve) are evaluated.

Pharmacodynamic Studies:

- Assesses the therapeutic effect of the drug delivered through the patch.
- For example, antihypertensive patches are evaluated for their effect on blood pressure.

Adhesion Performance:

- After application to the volunteers, the study measures the application of the transdermal patch with regard to time and a variety of conditions (e.g., exercise level, amount of perspiration).

5.5 Stability Studies

Stability studies allow for testing of the patch's performance and safety under a variety of storage conditions.

Accelerated Stability Studies:

- Patches are stored under accelerated stability conditions (i.e., 40 degrees Celsius, 75% relative humidity) for a specified time period.
- The patches are subject to evaluation of several parameters such as drug content, visual appearance, and adhesion over time.

Real Time Stability Studies:

- Real-time stability studies are conducted to establish the shelf life for the transdermal patch.

Regulatory Compliance:

- The evaluation of transdermal patches must follow standard guidelines and/or regulations established by regulatory authorities such as FDA, EMA, or ICH. These can include essential biocompatibility, safety, and efficacy testing for regulatory compliance.

6. Recent Innovations in Transdermal Drug Delivery Systems (TDDS)

he evolution of transdermal drug delivery systems is being accelerated by advances in nanotechnology, material science, and biomedical engineering. New technologies focus on the issues people face with traditional patches, namely, low permeability when using hydrophilic or high molecular weight drugs, and to improve target delivery, responsiveness and patient compliance.

6.1 Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers are the second generation of lipid-based systems, composed of both solid and liquid lipids, NLCs have the following beneficial characteristics:

- High drug capacity through the need to have imperfections in lipid matrices.
- Increased skin permeation by disorders in solid lipid matrices that result in possible interactions with stratum corneum lipids.
- Sustained release, controlled release.
- Low biological toxicity and high biocompatibility.

The transdermal patch delivery systems based on NLCs have shown promise for delivery of an anti-inflammatory agent, antifungal agents as well as anticancer agents [27].

6.2 Spanlastics and Ethosomes

Elastic vesicular systems Spanlastics and Ethosomes are designed to improve the delivery of hydrophilic drugs and those medicines that are lipophilic through the skin

- Spanlastics: non-ionic surfactant-based vesicles that have very high deformability and penetrating power.
- Ethosomes: vesicles based on phospholipids and contain mostly ethanol to cause disruption in intercellular lipid junctions for greater penetration.

These carrier systems are increasingly being embedded into film forming gels or patches for topical or transdermal delivery of drugs that have poor permeability [26].

6.3 Microneedle Arrays

Microneedles (MNs) are micron-sized minimally invasive devices that create temporary microchannels in the skin to allow direct diffusion of drug into the dermis.

Types of MNs: Solid, coated, dissolvable, hydrogel-forming

- MNs simplify drug delivery; painless to administer, punch through stratum corneum, can be used for peptides, vaccines and macromolecules
- Smart MN patches: Can include sensors for drug delivery feedback and controlled release

6.4 Dissolving and Hydrogel Microneedles

Dissolving microneedle systems and hydrogel-forming microneedles are made with biodegradable polymers, such as hyaluronic acid or PVA that dissolve upon insertion into the skin and do not create sharps waste [32].

- Hydrogel-forming microneedles create pores by absorbing interstitial fluid, allowing drug to diffuse from a patch reservoir directly into skin.
- Examples include insulin, hormone delivery, biologics.

6.5 Smart Transdermal Patches

The newest generation of transdermal patches includes electronic components and responsive materials:

- Sensor-based patches that monitor physiological parameters (glucose, temperature, sweat, etc).
- Stimuli-responsive systems that release drug based on pH stimulation, heat, or electric current.
- Wearable patches with Bluetooth / NFC capabilities that allow remote monitoring and dosage adjustments.

We can expect to see intelligent systems with increased precision and personalization, and of course, adherence.

6.6 3D Printing and Electrospinning in Patch Design

Advances in 3D printing methods and electrospinning, two innovative manufacturing methods, have the following advantages:

- A customizable patch design and structure.
- Nanofiber mats with a high surface area to promote fast release of drugs from patches.
- Layer-by-layer control over drug localization and kinetics.

These methods also increase formulation flexibility in manufacture; so it may be possible to load multiple drugs in the same patch or develop targeted release patterns.

6.7 Polymeric Innovations

The continued development of smart polymers e.g.:

- Thermosensitive (e.g. Pluronic® F127)
- pH-sensitive (e.g. Eudragit® polymers)
- Mucoadhesive and bioadhesive polymers for better skin adhesion

These materials improve patch effectiveness, especially at mucosal sites or difficult skin sites.

CONCLUSION

Transdermal drug delivery systems (TDDS) have successfully moved into the forefront of drug administered to patients. Some advantages of TDDS is that the potential for increased compliance with the treatment, avoiding first pass metabolism, and sustained drug release. Of the many approaches TDDS has taken, patches have emerged as the most popular due to their non-invasive and consistent therapeutic levels of drug delivery.

Recent advances in transdermal delivery—including nanocarriers, microneedles, and smart patches—have created significant improvements in the practical ability to deliver drugs through transdermal means. These advances enable improved skin permeability, targeted release of drug, and decreased side effects. Contemporary formulation and evaluation techniques, give an extra assurance of quality, safety, and therapeutic levels for transdermal systems. There are still barriers to maximizing the benefits of the transdermal patches, which include skin permeability variability, drug selection criteria, and scaling to larger manufacturing levels. the opportunities for the development of transdermal patches for dermatology and systemic therapy are substantial and increasing. Interdisciplinary research and innovation will drive the maximum potential of transdermal delivery to find more relevance in clinical practice.

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