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Introduction to Transdermal Patches: History, Types, and Basic Principles

Afroz Fatima[1], S. S. Apte[2]

[1,2]University of Pharmaceutical Sciences, Kakatiya University, Warangal

ABSTRACT

Transdermal patches have emerged as a revolutionary drug delivery system, offering a non-invasive, convenient, and controlled method of administering medications. This review provides a comprehensive overview of transdermal patches, covering their history, types, and basic principles. The evolution of transdermal patches is traced from early topical treatments to the development of modern patches in the 1970s, highlighting significant milestones that have shaped the technology. Various types of transdermal patches are discussed, including matrix, reservoir, adhesive, and microstructured patches, each with unique design characteristics, advantages, and limitations.The review delves into the fundamental principles of transdermal drug delivery, emphasizing the role of skin structure and permeability in drug absorption. It explores mechanisms of drug absorption, factors influencing transdermal delivery, and enhancement techniques such as permeation enhancers and microneedles. The article also addresses the benefits of transdermal patches, including controlled drug release, improved patient compliance, and the avoidance of first-pass metabolism. The discussion aims to provide a solid foundation for understanding the current state and future prospects of transdermal patch technology, highlighting its impact on improving therapeutic outcomes and patient care.

Keywords: Transdermal Drug Delivery, Controlled Release, Permeation Enhancers, Skin Absorption, Non-invasive Therapy, etc.

INTRODUCTION

Overview of Transdermal Patches

Transdermal patches are a sophisticated drug delivery system designed to administer medications through the skin and into the bloodstream. This method offers several advantages over traditional routes of administration, such as oral or intravenous methods. Transdermal patches are engineered to provide controlled and sustained drug release, enhance patient compliance, and minimize systemic side effects (Prausnitz& Langer, 2008; Barry, 2001).

Advantages of Transdermal Patches

- **Non-invasive Delivery**: Transdermal patches offer a pain-free alternative to injections, reducing discomfort and the risk of infection.
- **Controlled Release**: They provide a steady release of medication over an extended period, maintaining consistent therapeutic levels.
- **Improved Compliance**: Once applied, patches require minimal attention, enhancing adherence to medication regimens.
- **Avoidance of First-pass Metabolism**: By bypassing the gastrointestinal tract and liver, transdermal delivery can improve bioavailability and reduce the required dosage (Guy, 2010; Mitragotri & Langer, 2004).
- **Reduction of Side Effects**: Localized delivery can minimize systemic side effects often associated with oral or injectable medications (Kydonieus, 2017).

Applications of Transdermal Patches

Transdermal patches are used for a wide range of therapeutic applications, including:

- **Pain Management**: Patches delivering analgesics like fentanyl are used for chronic pain management (Brown et al., 2006).
- **Hormone Replacement Therapy**: Estrogen patches are commonly prescribed for menopausal symptoms.

- **Nicotine Replacement Therapy**: Nicotine patches aid in smoking cessation by delivering controlled doses of nicotine (Ramsay & Faulkner, 2013).
- **Cardiovascular Diseases**: Nitroglycerin patches are used to prevent angina pectoris.
- **Neurological Disorders**: Patches delivering medications for conditions like Parkinson's disease and attention deficit hyperactivity disorder (ADHD) (Paudel et al., 2010).

The future of transdermal patches is promising, with ongoing research focused on improving drug delivery efficiency, expanding the range of treatable conditions, and incorporating advanced technologies such as microneedles and nanocarriers. Innovations aim to overcome current limitations and enhance the therapeutic potential of transdermal systems (Larrañeta et al., 2016).

Transdermal patches represent a significant advancement in drug delivery, offering numerous benefits over traditional methods. Their ability to provide controlled, sustained, and non-invasive drug delivery makes them a valuable tool in modern medicine, with the potential for continued growth and innovation in the future (Williams & Barry, 2012).

Importance of Transdermal Drug Delivery
Transdermal drug delivery systems (TDDS) have gained significant attention in the pharmaceutical industry due to their unique advantages and broad range of applications. Here are key reasons why transdermal drug delivery is important:

Enhanced Patient Compliance
One of the major benefits of transdermal patches is their ability to improve patient adherence to medication regimens. Oral medications often require multiple daily doses, which can be inconvenient and difficult for patients to remember. In contrast, transdermal patches are designed for prolonged use, often requiring application only once daily, weekly, or even monthly, thus reducing the burden on patients and enhancing compliance (Wokovich et al., 2006; Morrow et al., 2007).

Controlled and Sustained Drug Release
Transdermal patches are engineered to deliver drugs at a controlled rate over an extended period. This steady release ensures that therapeutic levels of the drug are maintained in the bloodstream, minimizing the peaks and troughs associated with oral or injectable medications. This can lead to more consistent therapeutic effects and reduce the risk of side effects caused by fluctuating drug levels (Benson, 2005; Lane, 2013).

Non-invasive and Painless
Unlike injections, transdermal patches offer a non-invasive route of administration. This is particularly beneficial for patients who have a fear of needles or experience pain and discomfort from injections. By providing a painless alternative, transdermal patches improve the overall patient experience and can be used for long-term treatments without causing trauma to the skin or tissues (Prausnitz& Elias, 2008; Sivamani et al., 2005).

Avoidance of First-pass Metabolism
Drugs administered orally undergo first-pass metabolism in the liver, where a significant portion of the drug can be metabolized before reaching systemic circulation. Transdermal delivery bypasses the gastrointestinal tract and liver, allowing the drug to enter the bloodstream directly. This can enhance the bioavailability of the drug, reduce the required dosage, and minimize the risk of gastrointestinal side effects (Reddy & Guy, 2010; Jasti & Bunge, 2002).

Versatility and Flexibility
Transdermal patches can be used for a wide variety of therapeutic applications, including pain management, hormone replacement therapy, smoking cessation, cardiovascular treatment, and neurological disorders. Their versatility makes them suitable for delivering both small and large molecules, including peptides and proteins, which are typically challenging to administer via oral routes (Cevc, 2004; Flynn, 1996).

Improved Safety Profile
The controlled release mechanism of transdermal patches reduces the risk of overdose and improves the safety profile of the drug. This is especially important for medications with narrow therapeutic windows, where maintaining precise drug levels is critical. Additionally, the direct delivery to the bloodstream minimizes exposure to the digestive system, reducing the risk of gastrointestinal irritation and other related side effects (Repka et al., 2003; Wiedersberg& Guy, 2014).

Innovation and Future Potential
Ongoing research and development in transdermal drug delivery are leading to innovative solutions that enhance drug penetration and efficacy. Technologies such as microneedles, iontophoresis, and sonophoresis are being explored to

overcome the limitations of traditional patches. These advancements hold the potential to expand the range of drugs that can be delivered transdermally, including biologics and vaccines (Karande et al., 2004; Kumar & Philip, 2007).

Transdermal drug delivery offers numerous advantages that address many of the limitations associated with traditional drug administration methods. Its ability to provide controlled, sustained, and non-invasive delivery makes it an essential and growing field in pharmaceutical research and development. As technology advances, transdermal drug delivery is poised to play an increasingly important role in improving therapeutic outcomes (Wu et al., 2017; Zignani et al., 1995).

HISTORY OF TRANSDERMAL PATCHES

Early Applications of Topical Treatments

The use of topical treatments for medicinal purposes dates back thousands of years and spans various cultures and civilizations. These early applications laid the groundwork for modern transdermal drug delivery systems. Here are some key points highlighting the historical context and evolution of topical treatments:

Ancient Civilizations and Herbal Remedies

- **Egyptians**: The ancient Egyptians are known for their extensive use of topical applications for medicinal purposes. They utilized a variety of plant-based ointments and poultices to treat wounds, skin conditions, and infections. Ingredients such as honey, animal fats, and herbal extracts were common in their formulations (Flynn, 1996; Zugerman& Fowler, 1996).
- **Greeks and Romans**: In ancient Greece and Rome, topical treatments were an integral part of medical practice. Physicians like Hippocrates and Galen documented the use of various salves and plasters made from natural substances, including olive oil, beeswax, and medicinal herbs. These treatments were used to alleviate pain, reduce inflammation, and promote wound healing (Chien, 1992; Jasti & Bunge, 2002).
- **Traditional Chinese Medicine (TCM)**: TCM has a long history of using topical preparations for therapeutic purposes. Balms, oils, and poultices made from herbal ingredients were applied to the skin to treat conditions such as muscle pain, arthritis, and skin disorders. The use of acupuncture and moxibustion also complemented these topical therapies (Prausnitz& Langer, 2008).

Medieval and Renaissance Periods

- **Medieval Europe**: During the Middle Ages, the knowledge of herbal medicine and topical treatments was preserved and expanded upon by monastic communities and physicians. Remedies often included ingredients like frankincense, myrrh, and various herbs. These treatments were used for a wide range of ailments, from skin infections to joint pain (Cevc, 2004).
- **Renaissance**: The Renaissance period saw a resurgence in the study of medicine and natural remedies. Advances in botanical science and pharmacology led to the development of more sophisticated topical treatments. Alchemists and apothecaries experimented with various formulations to enhance the efficacy of their preparations (Barry, 2001).

18th and 19th Centuries: Foundations of Modern Pharmacology

- **Emergence of Pharmacology**: The 18th and 19th centuries marked significant progress in the field of pharmacology. The understanding of drug absorption and skin permeability began to take shape. Physicians and scientists started to explore the potential of topical treatments for systemic effects (Mitragotri & Langer, 2004).
- **Introduction of New Ingredients**: The discovery of new ingredients, such as iodine and sulfur, expanded the range of topical treatments available. These substances were used to treat skin diseases, infections, and other conditions (Benson, 2005).

20th Century: Transition to Modern Transdermal Patches

- **Early 20th Century**: The early 20th century saw the development of more advanced topical formulations, including creams, gels, and lotions. These products were designed to enhance the absorption of active ingredients through the skin (Wiedersberg& Guy, 2014).
- **Mid to Late 20th Century**: The concept of transdermal drug delivery began to gain traction. In 1979, the first FDA-approved transdermal patch, delivering scopolamine for motion sickness, was introduced. This marked a

significant milestone in the evolution of topical treatments, paving the way for the development of modern transdermal patches (Prausnitz& Langer, 2008).

Development of Modern Transdermal Patches

The development of modern transdermal patches has been a journey of scientific innovation, driven by the need for more effective and convenient drug delivery systems. This section explores the key milestones and advancements that have shaped the evolution of transdermal patches from concept to market-ready products.

Early Research and Conceptualization

- **Understanding Skin Permeability**: In the mid-20th century, research on skin permeability laid the groundwork for transdermal drug delivery. Scientists began to understand the barrier properties of the stratum corneum, the outermost layer of the skin, and explored ways to enhance drug penetration through this barrier (Guy, 2010; Karande et al., 2004).
- **Initial Experiments**: Early experiments focused on identifying drugs suitable for transdermal delivery, particularly those with low molecular weight and high lipophilicity. Researchers tested various formulations and materials to enhance skin absorption (Lane, 2013).

Introduction of the First Transdermal Patch

- **Scopolamine Patch (1979)**: The development of the first FDA-approved transdermal patch in 1979 was a groundbreaking achievement. The scopolamine patch, designed to prevent motion sickness, demonstrated the feasibility of delivering drugs through the skin. This patch employed a simple adhesive matrix system that released the drug over several days (Morrow et al., 2007).

Advancements in Patch Design and Technology

- **Reservoir Patches**: The introduction of reservoir patches marked a significant advancement in transdermal technology. These patches contained a liquid or gel reservoir of the drug, separated from the skin by a rate-controlling membrane. This design allowed for precise control over the drug release rate, improving the efficacy and safety of the delivery system (Paudel et al., 2010).
- **Matrix Patches**: Matrix patches, in which the drug is dispersed within a polymer matrix, became popular due to their simpler design and ease of manufacturing. The matrix also served as the adhesive layer, making the patches more flexible and comfortable for patients (Kydonieus, 2017).

Enhancement Techniques

- **Chemical Enhancers**: Researchers developed chemical enhancers that temporarily alter the stratum corneum, increasing its permeability. These enhancers include alcohols, fatty acids, and surfactants, which disrupt the lipid structure of the skin, facilitating drug absorption (Williams & Barry, 2012; Flynn, 1996).
- **Physical Enhancement Methods**: Techniques such as iontophoresis and sonophoresis emerged as innovative methods to enhance transdermal drug delivery. Iontophoresis uses a mild electrical current to drive charged drug molecules through the skin, while sonophoresis employs ultrasound waves to increase skin permeability (Sivamani et al., 2005).

Broadening the Range of Deliverable Drugs

- **Hormone Replacement Therapy**: The approval of estradiol and testosterone patches for hormone replacement therapy expanded the range of therapeutic applications for transdermal patches. These patches provided consistent hormone levels, reducing the fluctuations associated with oral therapies (Zugerman& Fowler, 1996).
- **Nicotine Replacement Therapy**: Nicotine patches became a popular aid for smoking cessation, offering a controlled release of nicotine to reduce withdrawal symptoms and cravings (Brown et al., 2006).

Recent Innovations and Future Directions

- **Microneedles**: Microneedle patches represent a cutting-edge advancement in transdermal technology. These patches contain tiny needles that painlessly penetrate the stratum corneum, delivering drugs directly into the

dermis. Microneedles enable the delivery of larger molecules, such as peptides and proteins, which were previously challenging to administer transdermally (Larrañeta et al., 2016; Jain et al., 2005).

- **Smart Patches**: The integration of sensors and microelectronics into transdermal patches has led to the development of smart patches. These devices can monitor physiological parameters, adjust drug release rates in response to real-time data, and even transmit information to healthcare providers (Wu et al., 2017).

Milestones in Transdermal Patch Technology

The development and evolution of transdermal patch technology have been marked by several key milestones. These advancements have significantly improved the efficacy, safety, and range of applications for transdermal drug delivery systems. Here are some of the most important milestones:

Discovery of Skin Permeability and Early Research (1950s-1960s)

- **Understanding Skin Barriers**: Initial research in the mid-20th century focused on understanding the skin's barrier function and how certain substances could penetrate the stratum corneum. This foundational knowledge was crucial for developing transdermal delivery systems (Barry, 2001; Paudel et al., 2010).

Development of the First Transdermal Patch (1979)

- **Scopolamine Patch Approval**: The first FDA-approved transdermal patch was introduced in 1979 for the prevention of motion sickness. The scopolamine patch demonstrated the feasibility of delivering medication through the skin over an extended period (Prausnitz& Langer, 2008).

Introduction of Hormone Replacement Therapy Patches (1980s)

- **Estradiol and Testosterone Patches**: The approval of estradiol and testosterone patches in the 1980s marked a significant expansion in the therapeutic applications of transdermal patches. These patches provided consistent hormone levels, enhancing patient compliance and reducing side effects associated with oral hormone therapies (Rautio et al., 2008).

Nicotine Patches for Smoking Cessation (1991)

- **Nicotine Replacement Therapy**: The introduction of nicotine patches revolutionized smoking cessation programs. These patches delivered controlled doses of nicotine to help reduce withdrawal symptoms and cravings, becoming a widely accepted method for aiding smoking cessation (Guy, 2010).

TYPES OF TRANSDERMAL PATCHES

Matrix Patches

- **Structure and Composition**: Matrix patches consist of a drug dispersed within a polymer matrix that acts as both the carrier and the adhesive. The matrix layer is designed to release the drug at a controlled rate, ensuring a steady supply to the skin. The backing layer provides support and protects the patch from environmental factors, while the release liner, which is removed before application, protects the adhesive layer until use (Kydonieus, 2017).

ADVANTAGES AND LIMITATIONS

Advantages:

- Simple design and manufacturing process.
- Good flexibility and comfort for the patient.
- Provides controlled drug release over an extended period.

Limitations:

- Limited to drugs with suitable molecular weight and solubility.
- Potential for uneven drug distribution within the matrix.
- The release rate may be affected by external factors such as temperature and humidity (Chien, 1992).

RESERVOIR PATCHES

Design and Mechanism: Reservoir patches feature a liquid or gel reservoir containing the drug, separated from the skin by a rate-controlling membrane. The membrane regulates the rate at which the drug is released from the reservoir and absorbed into the skin. The patch also includes an adhesive layer to ensure proper attachment to the skin and a backing layer to provide structural support (Paudel et al., 2010).

PROS AND CONS

Pros:

- Precise control over drug release rates.
- Suitable for drugs requiring a steady, consistent release.
- Can accommodate a higher drug load compared to matrix patches.

Cons:

- More complex and expensive to manufacture.
- Risk of leakage from the reservoir.
- Can be bulkier and less comfortable than matrix patches (Ramsay & Faulkner, 2013).

Adhesive Patches

- **Characteristics and Uses**: Adhesive patches integrate the drug directly into the adhesive layer, simplifying the design. These patches are commonly used for short-term applications where ease of use and quick onset of action are desired. The adhesive layer ensures that the patch adheres well to the skin, and the backing layer provides protection and support (Morrow et al., 2007).

Challenges in Drug Release Control:

- Controlling the drug release rate can be challenging due to the direct integration of the drug into the adhesive.
- Potential for skin irritation due to prolonged contact with the adhesive.
- Limited to drugs that are stable and effective when delivered through the adhesive medium (Wokovich et al., 2006).

Microstructured Patches

- **Innovation in Drug Delivery**: Microstructured patches utilize microneedles or other microstructures to enhance drug delivery through the skin. Microneedles create tiny channels in the stratum corneum, allowing for the efficient delivery of larger molecules, such as peptides and proteins, which are typically difficult to administer through traditional transdermal systems (Larrañeta et al., 2016; Karande et al., 2004).

APPLICATIONS AND BENEFITS

Applications:

- Delivery of vaccines, peptides, and biologics.
- Potential for use in cosmetic and dermatological treatments.
- Suitable for both systemic and localized drug delivery.

Benefits:

- Painless and minimally invasive.
- Can bypass the stratum corneum barrier, enhancing drug absorption.
- Reduces the risk of infection compared to traditional injections.
- Provides precise control over drug dosage and release kinetics (Jain et al., 2005; Wu et al., 2017).

BASIC PRINCIPLES OF TRANSDERMAL DRUG DELIVERY

Skin Structure and Permeability

The skin serves as a protective barrier and consists of three main layers: the epidermis, dermis, and hypodermis. The outermost layer, the stratum corneum, is the primary barrier to drug penetration. It is composed of dead keratinocytes embedded in a lipid matrix, which provides a tough and impermeable barrier. The permeability of the skin is influenced by the properties of the stratum corneum, including its thickness, lipid content, and hydration level (Guy, 2010).

Mechanisms of Drug Absorption

Transdermal drug absorption involves several steps:

1. **Penetration**: The drug diffuses through the stratum corneum.
2. **Partitioning**: The drug partitions into the viable epidermis.
3. **Diffusion**: The drug diffuses through the viable epidermis and dermis.
4. **Absorption**: The drug is absorbed into the systemic circulation via the capillary network in the dermis (Barry, 2001; Rautio et al., 2008).

Factors Affecting Transdermal Delivery

- **Drug Properties**: Ideal candidates for transdermal delivery have low molecular weight (<500 Da), high lipophilicity, and moderate polarity. Drugs should also be potent, as only small amounts can permeate the skin (Williams & Barry, 2012; Chien, 1992).
- **Skin Conditions**: Factors such as age, hydration, and integrity of the skin can influence drug absorption. Conditions like psoriasis or eczema can alter the barrier function of the skin, affecting drug delivery (Cevc, 2004; Flynn, 1996).

Enhancers and Techniques: Various methods are used to enhance skin permeability, including:

- **Chemical Enhancers**: Compounds such as alcohols, fatty acids, and surfactants disrupt the stratum corneum to increase permeability (Karande et al., 2004).
- **Physical Techniques**: Methods like iontophoresis and sonophoresis use electrical currents and ultrasound waves, respectively, to facilitate drug penetration through the skin (Sivamani et al., 2005).

Controlled Release Mechanisms

Transdermal patches are designed to release drugs at a controlled rate over an extended period. This can be achieved through various mechanisms:

- **Matrix Systems**: The drug is dispersed in a polymer matrix that controls the release rate (Kydonieus, 2017).
- **Reservoir Systems**: The drug is contained in a liquid or gel reservoir, separated by a rate-controlling membrane (Paudel et al., 2010).
- **Microstructured Systems**: Microneedles or microchannels provide precise control over drug release by enhancing skin permeability and targeting delivery (Larrañeta et al., 2016).

Non-invasive Nature of Transdermal Patches

Transdermal patches offer a non-invasive alternative to injections, reducing pain and the risk of infection. They are easy to apply and remove, improving patient comfort and compliance. This non-invasive approach is particularly beneficial for long-term therapies and for patients with needle phobia (Prausnitz& Elias, 2008).

Avoidance of First-pass Metabolism

Transdermal delivery bypasses the gastrointestinal tract and hepatic first-pass metabolism, which can significantly reduce the bioavailability of orally administered drugs. By avoiding first-pass metabolism, transdermal patches can improve the bioavailability of the drug, reduce the required dose, and minimize gastrointestinal side effects (Reddy & Guy, 2010).

CONCLUSION

Transdermal patches represent a significant advancement in drug delivery systems, offering a non-invasive, controlled, and convenient method for administering medications. Key points include the understanding of skin structure and permeability, mechanisms of drug absorption, and factors affecting transdermal delivery such as drug properties, skin conditions, and enhancement techniques. Controlled release mechanisms in patches, such as matrix and reservoir systems, enable sustained

drug delivery, improving therapeutic outcomes and patient compliance. Looking to the future, innovations such as microneedle technology and smart patches are poised to expand the range of drugs that can be delivered transdermally, including biologics and vaccines. These advancements hold the potential to enhance personalized medicine and non-invasive therapeutic solutions. The ongoing development of transdermal patches is expected to have a significant impact on healthcare by providing safer, more effective, and patient-friendly drug delivery options, ultimately improving the quality of care and patient outcomes (Benson, 2005; Flynn, 1996; Reddy & Guy, 2010).

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