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A REVIEW ON TRANSDERMAL PATCH

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ABSTRACT

A transdermal patch is a medicated adhesive patch that you place on your skin to deliver medication directly into your bloodstream. This method is part of a newer way to deliver drugs, which offers benefits over traditional methods like pills. Transdermal patches come in different sizes and can contain one or more active ingredients. This review provides important information about transdermal patches, including their advantages and disadvantages, how they work, the different types available, their basic components, methods of making them, how they are evaluated, and their uses. Many types of medications are now available in patch form.

INTRODUCTION

The transdermal drug delivery system has been around for a long time. In the past, people mostly used creams and ointments for skin issues, but these sometimes caused side effects because the medicine absorbed into the bloodstrem. Transdermal delivery includes any medication applied to the skin that aims to enter the bloodstream. These systems are designed for controlled, continuous release of drugs through the skin, avoiding painful injections and bypassing the liver's first-pass metabolism, which can reduce the drug's effectiveness.The main benefits of this system are the controlled release of medication and the fact that it's painless. A transdermal patch adheres to the skin and consists of several parts, such as liners, adhesives, drug reservoirs, and membranes, all of which help deliver the drug effectively.Different types of patches and application methods have been developed to enhance drug delivery. Because of these advantages, transdermal delivery has become an important area of research in drug delivery systems.

ADVANTAGES

Transdermal patches offer several advantages:

1. Steady Drug Delivery: They provide a controlled release of medication over time, maintaining stable drug levels in the bloodstream.
2. Convenience: Patches are easy to use and can be applied and removed without the need for injections or oral medications.
3. Reduced Side Effects: By bypassing the digestive system, transdermal patches can minimize

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gastrointestinal side effects and improve drug absorption.
4. Non-invasive: They offer a non-invasive alternative to injections, making them more acceptable for patients who fear needles.
5. Improved Adherence: The simplicity of use can enhance patient compliance with medication regimens.
6. Localized Treatment: Some patches can deliver medication directly to the site of action, reducing systemic exposure and potential side effects.
7. Long-lasting Effects: Many patches can provide extended relief for chronic conditions, reducing the need for frequent dosing.
8. Potential for Combination Therapies: Some patches can deliver multiple medications simultaneously, simplifying treatment for complex conditions.

DISADVANTAGES

Transdermal patches have several disadvantages, including:

1. Skin Reactions: Some users may experience irritation, redness, or allergic reactions at the application site.
2. Limited Drug Types: Not all medications can be effectively delivered through the skin due to molecular size or solubility issues.
3. Variable Absorption: Absorption rates can vary based on factors like skin thickness, temperature, and moisture levels, leading to inconsistent dosing.
4. Duration of Effect: Patches may not provide immediate relief, as they typically release medication slowly over time.
5. Cost: Transdermal patches can be more expensive than oral medications.
6. Displacement Issues: Patches may become dislodged or fall off, especially if exposed to moisture or friction.
7. Limited Dosing Flexibility: Once applied, it's challenging to adjust the dose quickly, unlike oral medications.
8. Potential for Systemic Side Effects: Medications delivered systemically can lead to side effects that may not occur with localized treatments.
9. Patient Compliance: Some patients may forget to change patches or may not follow the application guidelines properly.

STRUCTURE OF SKIN

The skin is composed of three primary layers, each with distinct structures and functions:

1. Epidermis

Outer Layer: The outermost layer, primarily made up of keratinized stratified squamous epithelium.

Cell Types: Contains keratinocytes (produce keratin), melanocytes (produce melanin), Langerhans cells (immune response), and Merkel cells (touch sensation).

Sub-Layers: Includes several sub-layers, such as the stratum corneum (outermost), stratum lucidum (found only in thick skin), stratum granulosum, stratum spinosum, and stratum basale (where new cells are generated).

2. Dermis

Middle Layer: Beneath the epidermis, the dermis provides structural support and strength.Components: Contains connective tissue, blood vessels, nerves, hair follicles, and glands (sweat and sebaceous).

Sub-Layers: Divided into the papillary dermis (upper layer with dermal papillae) and reticular dermis (deeper, thicker layer).

3. Hypodermis (Subcutaneous Layer)

Deepest Layer: Not technically part of the skin but lies beneath the dermis.

Function: Composed of loose connective tissue and fat, it provides insulation, cushioning, and energy storage, as well as anchors the skin to underlying structures.

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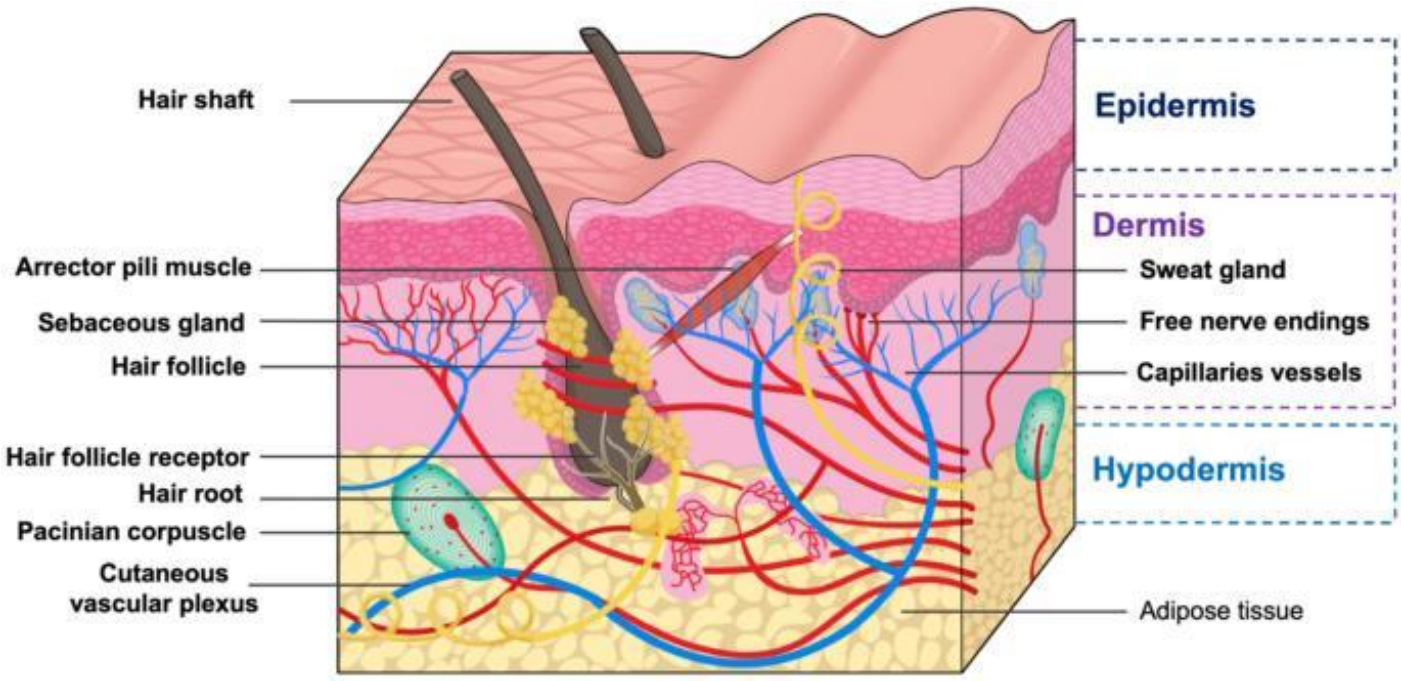

Figure No-02

PATHWAYS OF SKIN PERMEATION

Drug molecules can enter the skin through various pathways, including sweat ducts, hair follicles, and sebaceous glands, or directly across the outermost layer called the stratum corneum. Recently, scientists have debated the significance of these different routes, particularly the shunt (appendageal) pathway versus the direct pathway through the stratum corneum. This discussion is complicated by the absence of suitable experimental models to separate these pathways. A recent review by Menon offers useful insights into this topic. The stratum corneum is made up of 10 to 15 layers of cells called corneocytes.

TRANSDERMAL PATCH

A transdermal patch is a medicated adhesive patch that you place on your skin to deliver medication directly into the bloodstream. The first prescription patch approved by the U.S. Food and Drug Administration (FDA) was for scopolamine to treat motion sickness, available since December 1979. The most popular transdermal patch in the U.S. is the nicotine patch, which helps people quit smoking. The first vapor patch for reducing smoking was approved in Europe in 2007.

Many other transdermal patches are available, including:
Fentanyl Patches: Used for severe pain relief.
Nitroglycerin Patches: Help manage angina (chest pain).
Lidocaine Patches (Lidoderm): Relieve pain from shingles.
Buprenorphine Patches (Bu Trans): Provide pain relief for moderate to severe chronic pain and are sometimes used off-label for acute injuries.

Flector Patches (Diclofenac Epolamine): Nonsteroidal anti-inflammatory drug (NSAID) patches for treating acute pain from minor injuries and for chronic conditions like fibromyalgia and arthritis.

In 2005, the FDA began investigating reports of serious side effects, including deaths related to narcotic overdoses, specifically concerning the Duragesic fentanyl patch.

COMPONENTS OF TRANSDERMAL PATCHS

Transdermal patches consist of several key components:

1. **Backing Layer:** This is the outer layer that protects the patch and provides structural support. It's usually made from a polymer material.
2. **Drug Reservoir or Matrix:** This contains the active pharmaceutical ingredient (API). It can be in a liquid reservoir or a solid matrix form.
3. **Rate-Control Membrane:** This regulates the release of the drug from the reservoir into the skin.
4. **Adhesive Layer:** This allows the patch to adhere to the skin. It must be biocompatible and often contains a specific type of adhesive that ensures effective contact.
5. **Release Liner:** This is a protective layer that covers the adhesive before application, preventing premature adhesion.
6. **Permeation Enhancers (optional):** These are added to increase the skin's permeability to the drug, facilitating better absorption

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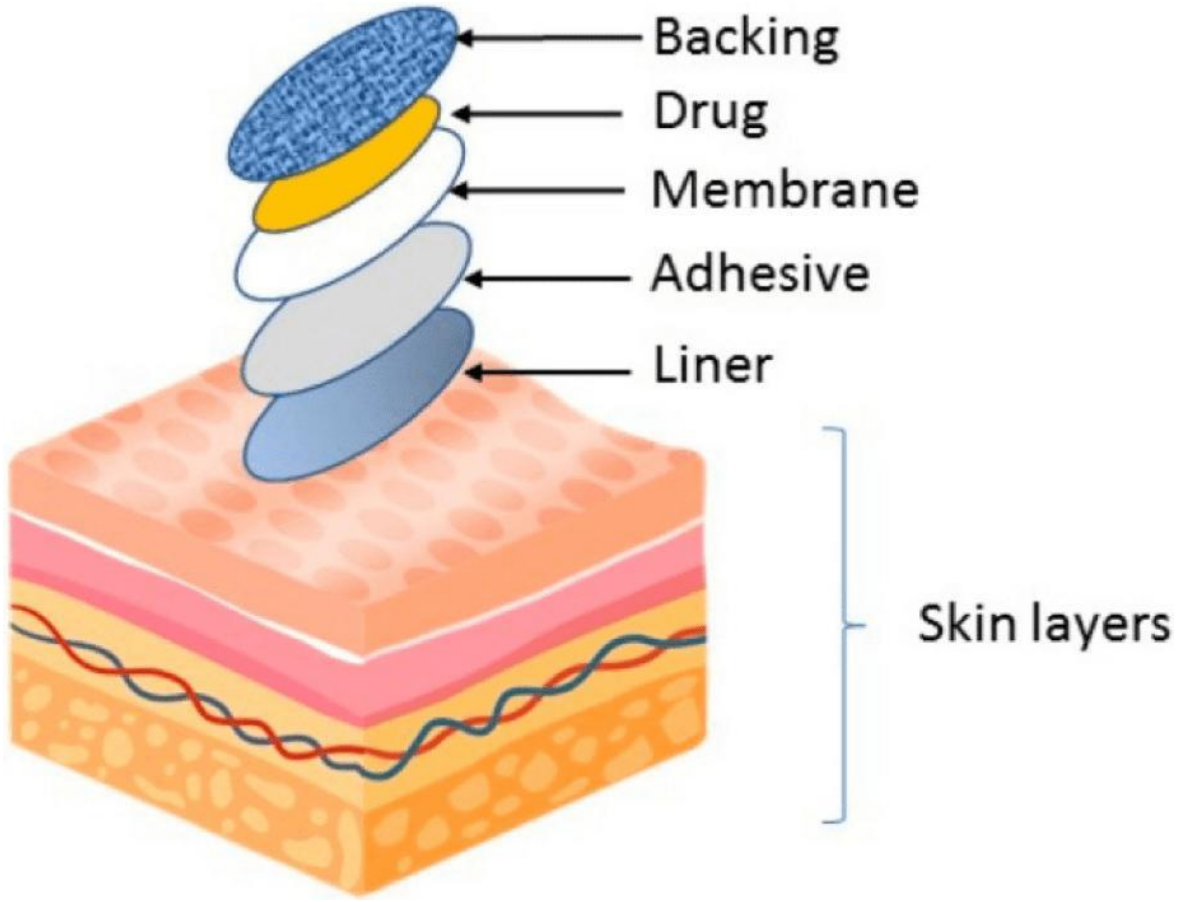

Figure no-03

1. Polymer Matrix
Polymers form the core of transdermal delivery systems. These systems typically consist of multilayer laminates with a drug reservoir sandwiched between two polymer layers:An outer layer that prevents drug loss.An inner adhesive layer that controls drug release and adheres to the skin.Choosing the right polymers is crucial for effectiveness, balancing release rates, adhesion, compatibility, and stability.

Types of Polymers
Natural Polymers: Cellulose derivatives, zein, gelatin, waxes, chitosan.
Synthetic Elastomers: Polybutadiene, silicon rubber, butyl rubber.
Synthetic Polymers: Polyvinyl alcohol, polyethylene, polyacrylate.

2. Drug Properties
The drug must have suitable physicochemical and pharmacokinetic properties for TDDS. This method is ideal for drugs that:Undergo extensive first-pass metabolism.Have a narrow therapeutic window.Require frequent dosing due to short half-lives.

3. Permeation Enhancers:
These substances increase skin permeability, allowing more drug absorption. They interact with skin components (like proteins and lipids) to improve drug delivery. Enhancers can help both oil-soluble and water-soluble drugs penetrate the skin better.

4. Pressure-Sensitive Adhesives (PSA)
PSAs ensure the patch stays in contact with the skin. They should adhere easily with light pressure and maintain a strong hold. Common PSAs include polyacrylates and silicon-based adhesives. The choice of adhesive depends on the patch design and drug formulation and should not interfere with drug release.

5. Backing Laminate
The backing layer provides structural support and must be chemically resistant to prevent interactions with the drug and other components. It should also ensure that no additives leach out during use.This simplified overview captures the key components and considerations for effective transdermal drug delivery systems.

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6. Backing Layer: The backing layer should have low moisture vapor transmission to keep the drug stable. It needs to be elastic, flexible, and strong enough to support the patch.

7. Release Liner

The release liner protects the drug during storage, preventing it from migrating into the adhesive and avoiding contamination. It acts as primary packaging, not as part of the dosage form.The release liner consists of:A base layer (which can be either non-occlusive or occlusive).A release coating layer made of materials like silicone or Teflon.Other materials for release liners can include polyester foil and metalized laminates.

8. Other Excipients

Various solvents (like chloroform, methanol, and acetone) are used to create drug reservoirs.Plasticizers (such as dibutyl phthalate and polyethylene glycol) are added to make the transdermal patch more flexible.This summary highlights the key elements related to backing layers, release liners, and additional excipients in transdermal drug delivery systems.

Types of Transdermal patches

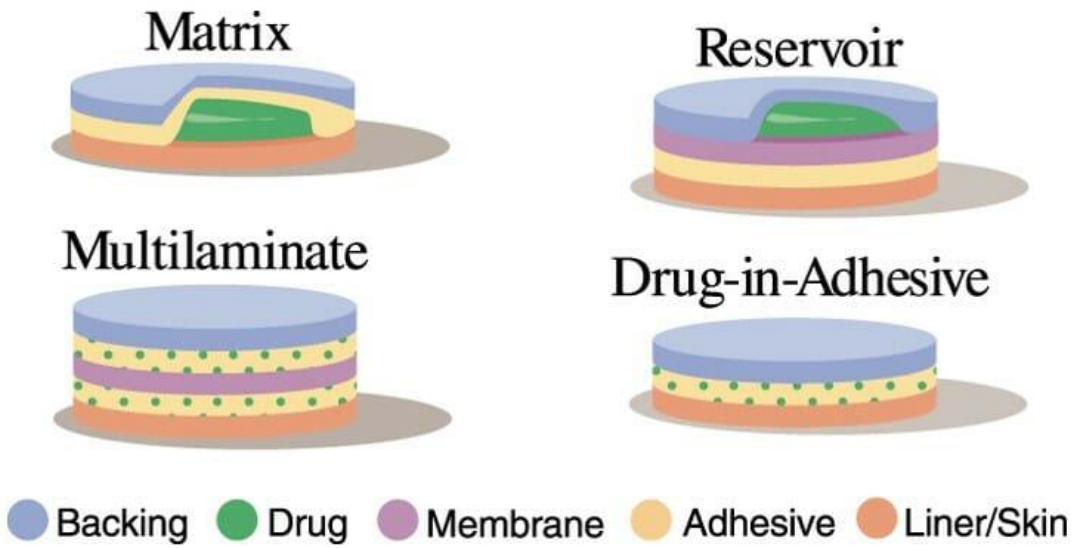

Figure No-04

1. Single-Layer Drug-in-Adhesive Patch

This patch has a layer of adhesive that contains the drug. The adhesive not only holds the patch together but also releases the drug onto the skin. It is covered by a temporary liner and a backing layer.

2. Multi-Layer Drug-in-Adhesive Patch

Similar to the single-layer patch, this type includes an immediate-release layer and a controlled-release layer, all within the adhesive. It also has a temporary liner and a permanent backing.

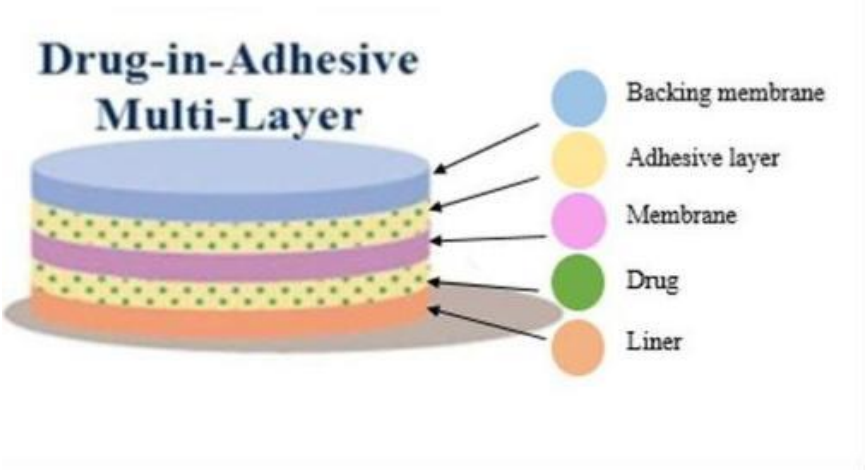

Figure No-05

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3. Vapor Patch
These patches release vapor instead of a solid drug. They are used for various purposes, such as delivering essential oils for congestion relief or improving sleep quality.

4. Reservoir System
In this system, the drug is contained in a reservoir between a non-permeable backing and a rate-controlling membrane, which can be porous or non-porous. The drug can be in various forms (solution, suspension, gel) and is held with a hypoallergenic adhesive on the outer surface.

5. Matrix System
Drug-in-Adhesive System: The drug is mixed with an adhesive to create a reservoir. This is then spread onto a non-permeable backing, protected by an additional adhesive layer. It can deliver multiple drugs and is known for its thin profile and good skin fit.

Matrix-Dispersion System: The drug is evenly mixed in a polymer matrix and formed into a medicated disc. This disc is then placed on an occlusive base, using a drug-impermeable backing layer.These systems are designed to enhance drug delivery through the skin, offering various benefits depending on their structure and formulation.

Micro Reservoir System: is a method for delivering drugs at a steady rate over time. It combines two types of drug delivery systems: the reservoir system and the matrix-dispersion system. First, a water-soluble polymer is mixed with the drug to create a reservoir. Then, this mixture is dispersed using high shear mechanical force into a lipophilic (fat-loving) polymer to form tiny, microscopic drug reservoirs. To stabilize the mixture and prevent it from breaking down, cross-linking agents are added, which help form stable bonds and keep the system intact. This allows the drug to be released at a consistent rate, maintaining constant drug levels.

METHOD OF PREPARATION OF TDDS

a) Asymmetric TPX membrane method.
b) Circular Teflon mould method.
c) Mercury substrate method.
d) By using IPM membranes" method.
e)By using "EVAC membranes" method.
f) Preparation of TDDS by using Proliposomes.
g) By using free film method.

a) Asymmetric TPX Membrane Method
discovered by Berner and John in 1994, involves creating a prototype patch using a heat-sealable polyester film (type 1009, 3M) as the backing membrane. The drug is spread on the concave surface of this membrane, which is then covered by an asymmetric TPX (poly(4-methyl-1-pentene)) membrane and sealed with an adhesive.

Preparation Process:The membrane can be prepared using either the dry or wet inversion method. For the wet method:

1. TPX is dissolved in a mixture of cyclohexane and non-solvent additives at 60°C to form a polymer solution.
2. The solution is then kept at 40°C for 24 hours.
3. Afterward, the polymer solution is cast onto a glass plate.
4. The casting film is dried at 50°C for 30 seconds.
5. The glass plate with the film is then immediately immersed in a coagulation bath at 25°C for 10 minutes.
6. After this, the membrane is removed and air-dried in a circulation oven at 50°C for 12 hours.

This process results in the formation of an asymmetric TPX membrane ready for use in creating drug delivery patches.

b) Circular Teflon Mould Method (Discovered by Baker and Heller, 1989)
A polymeric solution is prepared by dissolving a drug in one part and enhancers in another part.Both solutions are mixed together, and a plasticizer (like Di-N-butylphthalate) is added.The mixture is stirred for 12 hours and poured into a circular Teflon mould.The mould is covered with an inverted funnel to control solvent evaporation in a laminar flow hood (air speed of 0.5 m/s).The solvent is allowed to evaporate for 24 hours, and the dried film is stored for 24 hours at 25°C ± 0.5°C in a desiccator with silica gel before testing to avoid aging effects.

c) Mercury Substrate Method
The drug and plasticizer are dissolved in a polymeric solution and stirred for 10-15 minutes to form a homogeneous mixture.

The mixture is poured onto a levelled mercury surface and covered with an inverted funnel to control solvent evaporation.

d) IPM Membranes Method
The drug is dispersed in a mixture of water and a polymer (like propylene glycol with Carbomer 940) and stirred for 12 hours.The dispersion is neutralized by adding triethanolamine, and if the drug has poor solubility in water, a buffer (pH 7.4) is used to form a gel.This gel is then incorporated into the IPM membrane.

e) EVAC Membranes Method
For transdermal drug delivery systems (TDS), a 1% Carbopol gel is made using polyethylene (PE) and ethylene vinyl acetate copolymer (EVAC) as the rate-controlling membrane.If the drug is insoluble in water, propylene glycol is used to prepare the gel.The drug is dissolved in propylene glycol, and Carbopol is added and neutralized with sodium hydroxide.The drug gel is spread on a backing layer and covered with the rate-controlling membrane, then sealed to form a leak-proof device.

f) Preparation of TDDS by Using Proliposomes
Proliposomes are made using a film deposition technique with a drug-to-lecithin ratio of 0.1:2.0.Mannitol powder (5 mg) is dried in a round-bottom flask at 60-70°C while rotating.After drying, the flask temperature is lowered to 20-30°C.

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g) By Using Free Film Method

involves preparing a cellulose acetate-free film by casting it onto a mercury surface. Here's the simplified process:

1. Prepare the Polymer Solution: Dissolve 2% w/w polymer in chloroform, and add plasticizers at 40% w/w of the polymer weight.
2. Film Casting: Pour 5 ml of the polymer solution into a glass ring placed on a mercury surface inside a glass petri dish.
3. Control Evaporation: To control the rate of solvent evaporation, cover the petri dish with an inverted funnel.
4. Film Formation: Once the solvent evaporates completely, the film will form on the mercury surface.
5. Drying and Storage: After the film is dry, remove it and store it between sheets of wax paper in a desiccator until needed.By adjusting the volume of the polymer solution, films of different thicknesses can be created.The drug and lecithin are dissolved in an organic solvent, and 0.5 ml of the solution is added to the flask at 37°C.This process is repeated with additional solvent to complete the drying.

FACTORS AFFECTING TRANSDERMAL PATCH

There are various factors which affects the action of transdermal patches. These are given below:

a.Physicochemical Properties
i.Partition coefficient
ii. Molecular size
iii. Solubility/melting point
iv. Ionization
b. Physiological & Pathological Conditions of Skin
i.Reservoir effect of horny layer
ii. Lipid film
iii. Skin hydration
iv. Skin temperature
v. Regional variation
vi. Pathological injuries to the skin
vii. Cutaneous self-metabolism
viii. Skin barrier properties in the neonate and young infant
ix. Skin barrier properties in aged skin
x. Race
xi. Body site
xii. Penetration enhancers used [13]

PHYSICOCHEMICAL PROPERTIES

- Partition coefficient
- Molecular size
- Solubility/melting point
- Ionization

PHYSIOLOGICAL & PATHOLOGICAL CONDITION OF SKIN

- Reservoir effect of horny layer
- Lipid film
- Skin hydration
- Skin temperature
- Regional variation
- Pathological injuries to the skin
- Cutaneous self-metabolism
- Skin barrier properties in the neonate and young infant
- Skin barrier properties in aged skin

APPROACHES IN DEVELOPING TRANSDERMAL PATCH

1. Membrane-Controlled System

This type uses a membrane to control the release of the drug through the skin.

2. Adhesive Diffusion-Controlled System

In this system, the drug is released through an adhesive layer that controls how the drug diffuses through the skin.

3. Matrix Dispersion System

The drug is evenly dispersed within a matrix (a solid structure), and the drug is released as it diffuses through the matrix.

4. Microreservoir System

Tiny drug reservoirs are embedded in the patch, and the drug is released from these microreservoirs over time.

LIMITATIONS TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS)

1. Not all drugs are suitable: The drug must have specific physical and chemical properties to be effective for transdermal delivery.
2. Drugs needing high plasma levels: TDDS is not suitable for drugs that require high concentrations in the bloodstream.
3. Skin irritation: Drugs that cause skin irritation or contact dermatitis cannot be used in transdermal patches.
4. High molecular weight drugs: Drugs with large molecules are not suitable for transdermal delivery.
5. Metabolism through the skin: Drugs that are metabolized by the skin cannot be delivered effectively through this route.
6. Limited drug penetration: The skin is a strong barrier, so only drugs with low doses can be delivered transdermally.In summary, the transdermal route has limitations and is not suitable for all drugs, particularly those that require high doses or are prone to causing skin irritation.

RECENT ADVANCES IN TRANSDERMAL PATCH

1. Protein Delivery via Patch Technology

New patches are being developed to deliver proteins through the skin, providing a non-invasive alternative to injections.

2. Pain-Free Monitoring for Diabetes

Transdermal patches are now being used to monitor blood glucose levels in diabetics without the need for painful finger pricks.

3. Testosterone Patches for Women with Premature Ovarian Failure

A transdermal patch system is being used to deliver testosterone to young women with spontaneous premature ovarian failure to help manage symptoms.

4. Oxybutynin Patch for Overactive Bladder (OAB)

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Transdermal patches delivering oxybutynin are being used to treat overactive bladder, offering a more convenient treatment option.
5. Pain Relief through Transdermal Patches
Transdermal patches are being developed to provide localized pain relief, offering an alternative to oral pain medications.
6. Molecular Absorption Enhancement
New technologies are improving the skin's ability to absorb medications, making transdermal patches more effective in delivering various drugs.
This arrangement provides a clearer overview of current developments in transdermal patch technology.

CONCLUSION

The provides valuable information about transcutaneous drug delivery systems (TDDS) and methods for analyzing them, serving as a useful reference for those involved in TDDS research. The findings suggest that TDDS has great potential, capable of delivering both hydrophobic and water-soluble active ingredients. To fully optimize this drug delivery system, a deeper understanding of the biological interactions and mechanisms involved is necessary. TDDS holds promise as a practical solution for the next generation of drug delivery systems.

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