IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

ADVANCES IN TRANSDERMAL DRUG DELIVERY SYSTEMS

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Abstract: For thousands of years, human civilizations have used various substances on the skin for cosmetic and medicinal purposes. However, it wasn't until the 20th century that the skin began to be utilized as a drug delivery route. The term "transdermal," first recorded by Merriam-Webster in 1944, reflects the relatively recent development of this concept in medical and pharmaceutical fields. Transdermal drugs are self-contained, discrete dosage forms designed to deliver medication through the skin to achieve a systemic effect, ensuring consistent plasma drug levels without fluctuations. Topical administration of therapeutic agents offers several advantages over traditional oral or invasive drug delivery methods, including controlled release of the drug over an extended period. This review provides an overview of the advantages of transdermal drug delivery systems (TDDS), the skin's pathways for drug absorption, the key components of transdermal patches, and the approaches used in their preparation. Additionally, it covers the evaluation of transdermal systems, general clinical considerations in TDDS use, and the limitations of this drug delivery method.

Keywords: Transdermal drug delivery system, Control drug delivery system.

1. INTRODUCTION :

Drugs delivered via traditional dosage forms frequently result in noteworthy variations in plasma drug levels, which can result in undesirable side effects like toxicity or decreased efficacy. Factors such as repetitive dosing and unpredictable absorption have led to the advancement of controlled drug delivery systems.These systems are created to continuously release one or more drugs in a predetermined pattern over a fixed period, targeting either the entire body systemically, or a specific organ.The primary goals of controlled drug delivery are to enhance drug safety, effectiveness, and patient adherence by achieving improved regulation of plasma drug levels and reducing the need for frequent dosing.Transdermal therapeutic systems (TTS) are a form of controlled drug delivery method. They are self-contained, discrete dosage forms that, upon application to unblemished skin, release medications into the skin at a controlled pace, maintaining stable drug levels in the body's circulation.The initial Transdermal drug

delivery (TDD) system, Transderm-Scop, was developed in 1980. It contained the medication scopolamine and was used for treating motion sickness. The transdermal device is a membrane-moderated system.The membrane in this system is crafted from a microporous polypropylene film.The drug reservoir consists of the drug dissolved in a blend of mineral oil and polyisobutylene.This study release is extended over a three-day period.

2. PHYSIOLOGY OF THE SKIN :

The skin is the largest organ of the human body and serves as a vital protective barrier. It is composed of three primary layers: the epidermis, dermis, and hypodermis (subcutaneous tissue), each with distinct functions.

2.1. Epidermis: The outermost layer serves as the body's primary defense mechanism.It is mainly composed of keratinocytes and features the outermost sublayer, known as the stratum corneum, which plays a crucial role in preventing water loss and shielding against environmental elements. The epidermis hosts melanocytes, which generate melanin to shield against UV radiation.

2.2. Dermis: Beneath the epidermis lies the dermis, which is home to blood vessels, nerve endings, sweat glands, and hair follicles. It offers the skin both structural support and elasticity, courtesy of collagen and elastin fibers.The dermis has an essential function in regulating body temperature and experiencing sensations.

2.3. Hypodermis (Subcutaneous Tissue): The deepest layer of the skin, the hypodermis, is composed mainly of fat and connective tissue. It acts as an insulator, helping to conserve body heat, and cushions internal organs from trauma.

The skin graciously carries out numerous vital functions such as maintaining body temperature, perceiving external sensations, and expelling waste via sweat. In the realm of transdermal drug delivery, the skin functions as a selectively permeable barrier, facilitating the passage of specific medications through its outer layers to reach the bloodstream, all the while safeguarding the body from potentially harmful substances. Understanding the physiology of the skin is essential for the development of efficient transdermal drug delivery systems.

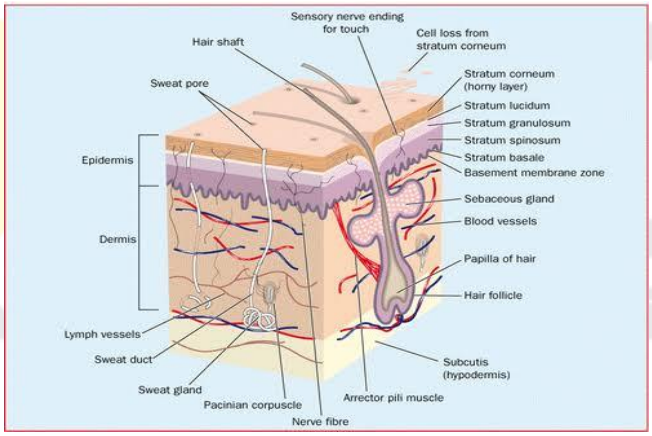

Fig. No.1: Anatomical and physiological Structure of skin

3. SKIN PATHWAYS FOR TRANSDERMAL DRUG DELIVERY SYSTEMS:

For transdermal drug delivery systems (TDDS), the skin serves as a selectively permeable barrier that allows certain drugs to penetrate and enter the bloodstream. The success of transdermal drug delivery depends on the drug's ability to traverse the skin layers. There are three primary pathways through which drugs can be absorbed:

3.1. Transcellular (Across Cells) Pathway:

In this pathway, the drug molecules pass directly through the cells of the epidermis, particularly the keratinocytes. Since the drug must traverse the lipid-rich cell membranes and water-rich cell interiors, this route can be challenging for drugs that are not both lipophilic and hydrophilic. The transcellular route often requires penetration enhancers to improve the drug's ability to cross cell membranes.

3.2. Intercellular (Between Cells) Pathway:

In the intercellular pathway, drugs diffuse between the cells of the stratum corneum, the outermost layer of the epidermis. This pathway is considered the most common route for transdermal drug delivery. The drug must navigate through the lipid-rich spaces between cells, making this pathway more favorable for lipophilic drugs. However, hydrophilic drugs may face more resistance due to the lipid nature of these spaces.

3.3.Transappendageal (Through Skin Appendages) Pathway:

This pathway involves drug absorption through skin appendages like hair follicles, sweat glands, and sebaceous glands. Although these appendages cover only a small portion of the skin's surface area, they provide a direct route to the dermis, bypassing the outer epidermal barrier. This pathway is especially important for drugs with larger molecular sizes or th passing through the the other two pathways.

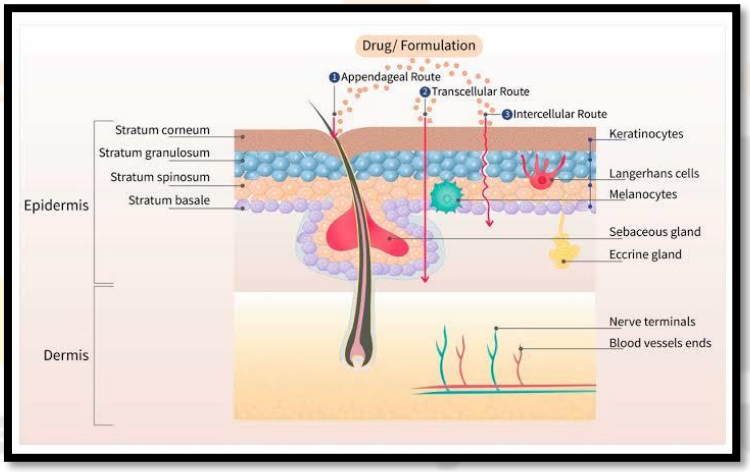

Fig.No.2: Pathways For Permeation Of Drug Across The Skin Barrier

4. TRANSDERMAL DRUG DELIVERY SYSTEMS:

Transdermal Drug Delivery Systems (TDDS) are specialized methods for administering drugs through the skin to achieve systemic therapeutic effects. Unlike conventional drug delivery methods, such as oral or injectable routes, TDDS deliver medication at a controlled rate directly into the bloodstream, bypassing the gastrointestinal system. This approach offers several advantages, including improved patient compliance, consistent drug levels, and reduced side effects due to more stable plasma concentrations[18].

4.1. Mechanism of Action:

When a TDDS is applied to the skin, the drug molecules pass through the outer skin layers via one or more pathways (transcellular, intercellular, or transappendageal). The drug enters the dermal blood vessels and is then absorbed into the systemic circulation.

4.2. Advantages of TDDS:

4.2.1. Sustained Release: Provides continuous drug delivery over a prolonged period, which can improve therapeutic effectiveness and minimize side effects.

4.2.2. Improved Patient Compliance: Reduces the frequency of dosing, making it easier for patients to adhere to treatment regimens.

4.2.3. Reduced Systemic Side Effects: Maintains stable drug levels, which can decrease the occurrence of adverse effects associated with peak plasma concentrations.

4.3. Disadvantages of TDDS:

4.3.1. Limited Drug Types: Not all drugs can be effectively delivered transdermally. Drugs must have appropriate molecular size, weight, and lipophilicity to penetrate the skin barrier.

4.3.2. Skin Sensitivity: Some patients may encounter irritation or allergic reactions at the application site.

4.3.3 Dose Limitations: The skin's permeability can limit the total amount of drug that can be delivered, making TDDS less suitable for high-dose therapies.

4.4. Recent Advances in TDDS:

4.4.1. Microneedles: Tiny needles that create microchannels in the skin to enhance drug penetration and enable the delivery of larger molecules.

4.4.2. Iontophoresis: Use of electrical currents to facilitate the transport of charged drugs across the skin.

4.4.3. Nanotechnology: Use of nanoparticles and nanocarriers to improve drug solubility, stability, and penetration through the skin barrier.

4.4.4. Smart Patches: Incorporation of sensors and actuators to monitor physiological conditions and adjust drug delivery accordingly.

4.4.5. Bioadhesive Systems: Advanced adhesives that enhance the adhesion and comfort of patches, improving usability.

4.5. BASIC COMPONENETS OF TRANSDERMAL DRUG DELIVERY SYSTEMS:

The components of Transdermal device include[5,7]:

A. Polymer matrix
B. Drug
C. Permeation enhancers
D. Other excipients

4.5.1. Polymer matrix:

This serves as the primary structure of the transdermal patch, providing mechanical strength and controlling the release of the drug. Commonly used polymers include polyethylene, polyvinyl chloride, and ethylene-vinyl acetate copolymers. The choice of polymer affects the drug release rate and the patch's adhesion to the skin.

4.5.1 Drug:

The active pharmaceutical ingredient (API) is the drug intended for systemic delivery. It must have suitable physicochemical properties (e.g., appropriate molecular weight, solubility, and partition coefficient) to facilitate absorption through the skin barrier.

4.5.2 Permeation enhancers:

These are substances added to improve the skin's permeability to the drug. They can facilitate the diffusion of the drug through the stratum corneum, the outermost layer of the skin. Common permeation enhancers include fatty acids, alcohols, and surfactants.

4.5.3 Other excipients:

These may include various additives to enhance the stability, solubility, and release characteristics of the drug. They can also help in the adhesion of the patch to the skin and include plasticizers, stabilizers, and fillers.

4.6 Additional Considerations:

4.6.1 **Backing Layer:** This protects the patch from the environment and provides structural integrity.

4.6.2 **Release Liner:** A protective layer that is removed before application, preventing the drug from being released prematurely.

4.6.3 **Adhesive Layer:** This layer adheres the patch to the skin, ensuring that it remains in place during use.

4.7 DESIGN OF TRANSDERMAL DELIVERY SYSTEM:

The design of a transdermal delivery system involves several fundamental components, primarily consisting of a drug that is either dissolved or dispersed within an inert polymer matrix. This matrix serves as the support structure and platform for drug release.

There are two primary designs of patch systems that determine the drug release characteristics and the overall behavior of the patch:

4.7.1. Matrix or Monolithic Design: In this configuration, the inert polymer matrix interacts directly with the drug, effectively binding it and controlling its release from the device. The drug diffuses through the polymer matrix at a rate dictated by the polymer's properties and the concentration of the drug.

4.7.2. Reservoir or Membrane Design: Unlike the matrix system, this design does not rely on the polymer matrix to control drug release. Instead, it incorporates a rate-controlling membrane situated between the drug reservoir and the adhesive layer. This membrane acts as the rate-limiting barrier, regulating the rate at which the drug is released from the device into the skin[12].

4.8. TECHNOLOGIES FOR DEVELOPING TRANSDERMAL DRUG DELIVERY SYSTEMS:

Several technologies have been effectively devised to regulate the rate of drug release and skin permeation.These technologies can be categorized into four fundamental approaches.

4.8.1. Polymer membrane permeation-controlled TDD Systems:

In this transdermal drug delivery system, the drug reservoir is situated between a drug-impermeable metallic plastic laminate and a rate-controlling polymeric membrane. Drug molecules are allowed to release solely through the rate-controlling polymeric membrane, which can be either a microporous or nonporous type. Common examples of such membranes include ethylene-vinyl acetate copolymer, which is designed to facilitate drug permeability. To enhance the system's adhesion and ensure effective contact with the skin surface, a thin layer of a drug-compatible, hypoallergenic pressure-sensitive adhesive polymer, such as silicone adhesive, is applied to the external surface of the polymeric membrane. This configuration ensures that the TDD system adheres closely to the skin while maintaining controlled drug release[15,19].

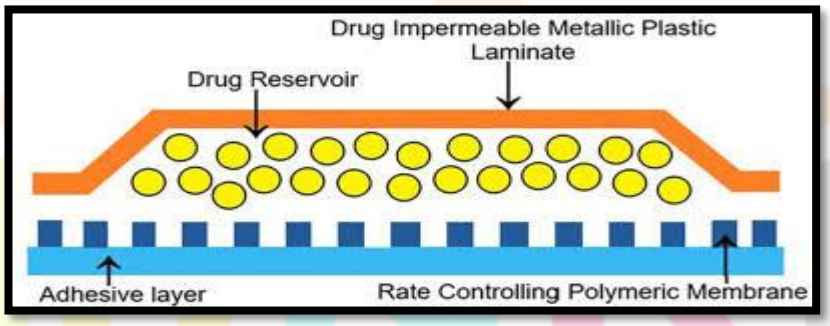

Fig.No.3: Polymer membrane permeation-controlled TDD Systems

4.8.2. Polymer matrix Diffusion-Controlled TDD Systems:

In diffusion-controlled transdermal drug delivery (TDD) systems utilizing a polymer matrix, the drug reservoir is created by evenly dispersing drug particles within a hydrophilic or lipophilic polymer matrix. This polymer mixture is then shaped into medicated disks with a specific surface area and thickness, designed for controlled drug release. These medicated disks are attached to an occlusive base plate, housed within a compartment made from drug-impermeable plastic backing. The system also features an adhesive polymer strip applied around the edge of the patch, forming an adhesive rim that encircles the medicated disk. Examples of such systems include the Nitro-Dur and NTS systems[21]

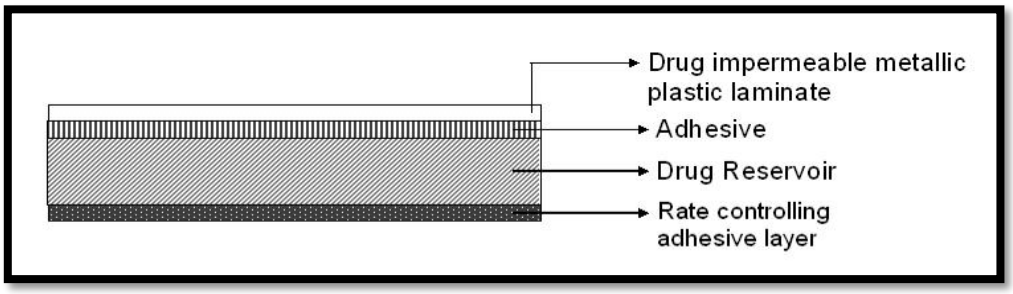

Fig.No.4: Polymer matrix Diffusion-Controlled TDD System

4.8.3. Drug Reservoir Gradient-Controlled TDD Systems:

In gradient-controlled transdermal drug delivery (TDD) systems, the drug reservoir is designed to address the limitations of non-zero-order drug release profiles seen in traditional matrix systems. In these systems, the drug loading within the polymer matrix is varied in an incremental manner, creating a concentration gradient. This gradient allows the drug to be released more consistently over time as it diffuses along the path across the multilaminate adhesive layer. By modifying the drug concentration along the diffusional path, the system achieves a more controlled and sustained drug release, resembling zero-order kinetics. This approach ensures a stable and prolonged delivery of the drug into the bloodstream, optimizing therapeutic effectiveness and minimizing peaks and troughs in drug levels. These systems can be further tailored to specific drug properties and desired release rates, making them highly adaptable for various clinical needs[24].

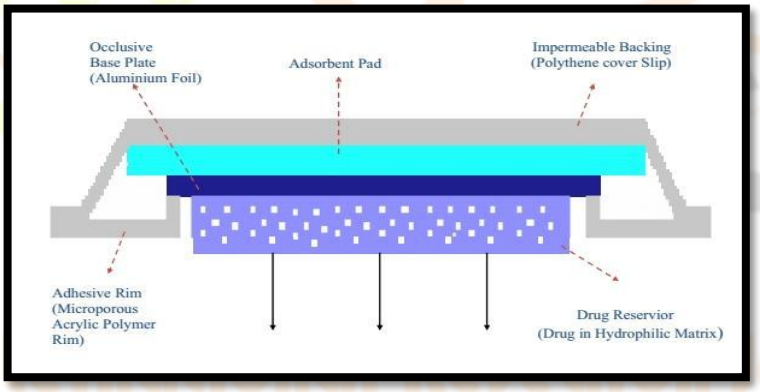

Fig.No.5: Drug Reservoir Gradient-Controlled TDD Systems

4.8.4. Microreservoir Dissolution-Controlled TDD Systems:

Microreservoir dissolution-controlled transdermal drug delivery (TDD) systems are a hybrid between reservoir and matrix dispersion systems.In this approach, the drug reservoir is established by suspending drug solids in an aqueous solution of a water-miscible solubilizer, such as polyethylene glycol.The suspension is evenly distributed within a lipophilic polymer through the application of high shear mechanical forces, resulting in the creation of numerous microscopic drug reservoirs.These microreservoirs, with their controlled aqueous solubility, are evenly spread within the polymer matrix.Given the thermodynamic instability of this dispersion, it undergoes rapid stabilization via the in situ cross-linking of polymer chains.This process involves forming a medicated polymer disc with a consistent surface area and thickness, guaranteeing a steady and controlled drug release.The tiny drug reservoirs nestled within the polymer ensure a continuous release as the drug dissolves and disperses through the polymer gradually, blending the advantages of matrix and reservoir systems.[22].

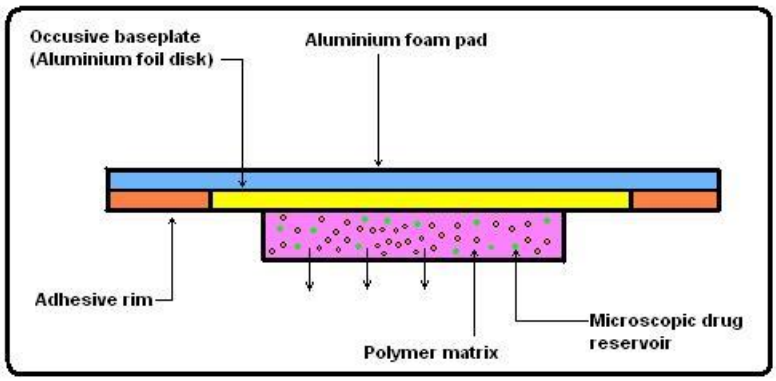

Fig.No.6: Microreservoir Dissolution-Controlled TDD Systems

5. PREPARATION OF TRANSDERMAL PATCHES:

Transdermal drug delivery patches can be prepared by Various methods:

5.1. The Mercury Substrate Method:

The Mercury Substrate Method is used to prepare drug-loaded polymer films. In this method, the drug is dissolved in a pre-measured amount of polymer solution, along with a plasticizer. The mixture is stirred thoroughly to form a homogeneous dispersion, and it is left undisturbed until all air bubbles are completely removed. Once the solution is ready, it is poured into a glass ring placed on a mercury surface inside a glass petri dish. To control the solvent's evaporation rate, an inverted funnel is placed over the petri dish. After the solvent evaporates, the dried films are collected and stored in a desiccator to prevent moisture absorption and ensure stability. This technique ensures controlled film formation, which can be used in various drug delivery applications.

5.2. The Glass Substrate Method:

The Glass Substrate Method is a technique used to prepare polymeric drug-loaded films. In this process, polymeric solutions are first left to swell, after which the required amounts of plasticizer and drug solution are added. The mixture is stirred for about 10 minutes to ensure uniform distribution, and then allowed to sit for a while to remove any trapped air bubbles. The resulting solution is carefully poured into a clean, dry petri plate. To control the evaporation rate of the solvent, a glass funnel is inverted over the petri plate. The solution is left to dry overnight, and once the films are fully dried, they are removed and stored in a desiccator to maintain stability and protect them from moisture. This method is commonly used in the development of thin films for drug delivery systems.

5.3. The Circular Teflon Mould Method:

The Circular Teflon Mould Method is employed to create drug-loaded polymer films using organic solvents. In this method, polymer solutions with various ratios are prepared in an organic solvent. The required amount of drug is dissolved in half of the same solvent, and a plasticizer is added to the drug-polymer solution. The mixture is stirred thoroughly to achieve a homogenous blend, which is then poured into a circular Teflon mould. To control the rate of solvent evaporation, an inverted glass funnel is placed over the Teflon mould. The solution is left to dry for 24 hours, allowing the solvent to evaporate gradually. Once the films are fully dried, they are carefully removed and stored in a desiccator to maintain stability and prevent moisture absorption. This method ensures precise film formation, often used in pharmaceutical applications for controlled drug release.

6. USES OF TDDS:

Transdermal Drug Delivery Systems (TDDS) are widely used in different medical situations,providing a gentle method for consistently delivering medications. Common uses include:

6.1. Pain Management: Patches containing opioids (e.g., fentanyl) or non-opioid analgesics are used for chronic pain management, especially in patients who have difficulty with oral medication.

6.2. Hormone Replacement Therapy (HRT): Estrogen and testosterone patches are used for hormone replacement therapy in conditions like menopause or hypogonadism, providing a steady release of hormones.

6.3. Nicotine Replacement Therapy (NRT): Nicotine patches are used to help people quit smoking by delivering controlled amounts of nicotine to reduce withdrawal symptoms and cravings.

6.4. Hypertension: Certain antihypertensive medications, such as clonidine, are available in transdermal formulations to manage high blood pressure.

6.5. Angina Pectoris: Nitroglycerin patches are used to prevent angina attacks by delivering a steady dose of the drug, which helps to relax blood vessels and improve blood flow.

6.6. Neurological Conditions:

6.6.1. Parkinson's disease: Patches containing drugs like rotigotine are used to manage motor symptoms in patients with Parkinson's disease.

6.6.2. Alzheimer's disease: Rivastigmine transdermal patches are delicately applied to help alleviate symptoms of Alzheimer's disease and release the medication slowly over an extended period of time**.**

6.7. Contraception: Hormonal patches containing a combination of estrogen and progestin are used as a method of birth control, providing a steady dose of hormones to prevent pregnancy.

6.8. Motion Sickness: Scopolamine patches help in preventing nausea and vomiting that are linked to motion sickness. The patch enables continuous release of its contents, ensuring lasting effectiveness.

6.9. Attention Deficit Hyperactivity Disorder (ADHD): Transdermal formulations of medications like methylphenidate are used to treat ADHD in children and adults, offering the benefit of controlled drug release.

6.10. Management of Overactive Bladder: Patches delivering oxybutynin are used to treat symptoms of overactive bladder, including frequent urination, urgency, and incontinence.

6.11. Migraines: Some migraine medications, such as sumatriptan, are delivered through patches to provide relief during acute migraine attacks.

7. LIMITATIONS FOR SELECTION OF TDDS:

All types of drugs cannot be administered through this route; the drug must have some desirable Physico-Chemical properties.

7.1. Drug Properties: Not all drugs can be administered transdermally. The drug must possess favorable physicochemical properties, such as low molecular weight, suitable lipophilicity, and adequate permeability

7.2. Plasma Level Requirements: TDDS is not suitable for drugs that require high plasma concentrations. The system is typically effective for delivering low to moderate doses.

7.3. Skin Irritation: Drugs that cause skin irritation or contact dermatitis cannot be delivered transdermally, as this would compromise patient comfort and compliance.

7.4. Molecular Weight: High molecular weight drugs are generally not suitable for transdermal delivery due to poor skin permeability.

7.5. Metabolism: Drugs that undergo significant metabolism in the skin or prior to reaching systemic circulation may not be effective when delivered via this route.

7.6. Skin Barrier: The skin acts as a strong barrier to drug penetration, limiting the types of drugs that can be effectively delivered transdermally, particularly in large doses.

8. EVALUATION TEST OF TRANSDERMAL PATCH:

8.1. Drug Content: A specified area of the patch is to be dissolved in a suitable solvent of a specific volume. The solution is then filtered through a filter medium, and the drug content is analyzed using an appropriate method, such as UV spectrophotometry or HPLC. The results are reported as the average value of three samples to ensure consistency and accuracy in the drug dosage contained within the patch.

8.2. Weight Uniformity: The prepared patches are dried at 60°C for 4 hours before testing. Specific areas of the patch are cut from different parts, weighed on a digital balance, and the average weight is calculated along with the standard deviation. This ensures uniformity in weight across different areas of the patch, which is essential for consistent dosing.

8.3. Thickness of the Patch: The thickness of the drug-loaded patch is measured at various points using a digital micrometer. The average thickness and standard deviation are determined to ensure uniformity in thickness, which is important for the patch's overall performance and drug release.

8.4. Flatness Test: Three longitudinal strips are cut from different sections of each film, one from the center, one from the left, and one from the right side. The length of each strip is measured, and any variation in length due to non-uniformity is assessed by calculating the percentage constriction. A 0% constriction corresponds to complete flatness.

8.5. Percentage Moisture Uptake: The films are initially weighed and then placed in desiccators at room temperature for 24 hours, where they are exposed to a saturated solution of

potassium chloride to maintain a relative humidity of 84%. After 24 hours, the films are reweighed, and the percentage of moisture uptake is calculated using the formula:

$$\text{Percentage moisture uptake} = [\text{Final weight-Initial weight/ Initial weight}] \times 100.$$

8.6. Moisture Loss: Each film is first weighed separately before being carefully placed in a desiccator with calcium chloride at a temperature of 40°C for a duration of 24 hours. Following this period, the films undergo reweighing where the percentage of moisture loss is determined using a specific formula**:**

$$\% \text{ Moisture Loss} = [\text{Initial wt} - \text{Final wt/ Final wt}] \times 100$$

8.7. Skin Irritation Study: Skin irritation and sensitization testing can be conducted on healthy rabbits weighing between 1.2 and 1.5 kg. The dorsal surface of the rabbit, covering an area of 50 cm^2, is cleaned, and the hair is removed by shaving. The area is further cleaned with rectified spirit. The test formulations are then applied to the cleaned skin. After 24 hours, the patch is removed, and the skin is examined for signs of irritation. The severity of the skin injury is assessed and classified into five grades based on the level of irritation observed.

9. CONCLUSION:

Transdermal drug delivery offers a painless, convenient, and effective method for administering consistent doses of various medications. This approach allows for a wide range of drugs to be delivered with enhanced absorption, minimal complications, and fewer side effects, making it cost-effective and user-friendly. For example, over a decade ago, the nicotine patch transformed smoking cessation, and transdermal systems were also being used for treatments such as nitroglycerin for angina, clonidine for hypertension, scopolamine for motion sickness, and estradiol for hormone replacement, benefiting millions of patients annually. One key advantage of transdermal delivery is that it bypasses the liver's first-pass metabolism, a limitation of many oral drugs. While dermal patches are the most common transdermal delivery method, challenges remain due to the skin's outer stratum corneum, which acts as a barrier to drug penetration. Researchers are continuously exploring physical and chemical methods to improve drug permeability through the skin.

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