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Recent Advancement in Transdermal Drug Delivery System

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ABSTRACT
The transdermal route offers several advantages over traditional drug delivery methods. These include high bioavailability, avoidance of first-pass liver metabolism, consistent drug levels in the bloodstream, and a non-invasive approach to treatment. Furthermore, transdermal drug delivery systems (TDDS) offer prolonged therapeutic effects, fewer side effects, enhanced bioavailability, improved patient adherence, and easy discontinuation of therapy. TDDS is used not only in pharmaceuticals but also in skincare and cosmetics. Research has shown that the transdermal route causes minimal skin irritation and performs better in various in vivo tests compared to oral administration. This review article provides an in-depth analysis of TDDS, emphasizing its benefits over conventional dosage forms, discussing limitations, examining transdermal patch components, exploring various patch types, outlining preparation methods, and identifying ideal TDDS requirements. Additionally, it addresses regulatory factors, physicochemical evaluation methods, therapeutic applications, and recent progress in transdermal drug delivery systems.

Keywords: Tdds; Transdermal Patch; Permeation Enhancer; Partition Coefficients; Iontophoresis**.**

I. INTRODUCTION

Transdermal drug delivery systems (TDDS), often called patches, offer a unique way to administer medications through the skin. These patches are designed to effectively deliver therapeutic amounts of drugs into the bloodstream, allowing for efficient treatment and prevention of various health conditions. A transdermal patch is a medicated adhesive that sticks to the skin, releasing precise doses of medication, which can also aid in healing targeted areas. Compared to oral, intravenous, subcutaneous, or transmucosal methods, this delivery route provides more consistent drug levels and reduces side effects, overcoming challenges linked with traditional pills or injections.

Transdermal systems are ideal for conditions that need long-term, frequent dosing, as they're less invasive, pain-free, and can be used independently by patients, making them both convenient and cost-effective. These systems are tailored to deliver drugs through the epidermis or dermis, effectively managing skin-related conditions by bypassing first-pass metabolism and allowing controlled release over time. The primary aim is to achieve a steady and predictable drug release rate, reducing patient-to-patient variability. Historically, early transdermal systems used drug-infused patches with natural adhesives to help drugs absorb through the skin.

This review highlights recent progress in developing chemical permeation enhancers and carriers, such as gels, emulsions, and vesicular systems, that improve the effectiveness of transdermal drug delivery.

1. Advantages of TDDs

- It allows for a continuous and stable release of medication over a prolonged period, minimizing the chances of side effects and treatment failures that can occur with intermittent dosing.
- These systems enable patients to administer the medication on their own.
- Transdermal delivery prevents the variations in drug levels that occur with peak and trough cycles, permitting extended and less frequent dosing.
- It provides a quicker and more convenient way to administer medication.
- The rate of absorption can be managed through a layered design.
- It avoids issues related to gastrointestinal compatibility.
- Patients are more likely to follow their treatment plans, as they are not required to take multiple doses daily.

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- This method allows patients to take control of their medication management independently.

.2. Disadvantages of TDDs

- For a drug to be suitable for transdermal delivery, it needs certain physicochemical characteristics to penetrate the stratum corneum. If the required dose is over 10 mg daily, effective transdermal delivery can become difficult.
- At present, only small, lipophilic drugs can be effectively transported through the skin.
- Transdermal administration offers extended drug release, but it can be costly due to the complex formulations involved.
- Drugs with low solubility, limited stability, short half-lives, or sensitivity to oxidation and hydrolysis present challenges, adding to manufacturing costs.
- There are limitations in the amount of medication that transdermal systems can carry.
- Transdermal delivery might result in lower drug levels in the bloodstream due to variations in skin barrier function, which can be influenced by factors like skin location and patient age..

- **Anatomy And Physiology of Skin**

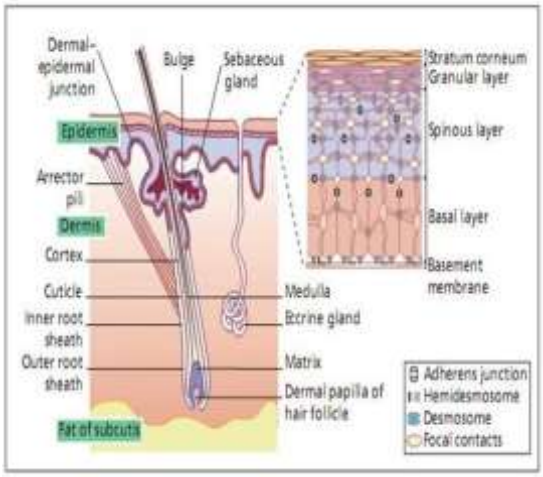

Figure 1 Anatomy and physiology of skin [20]

The skin acts as the body's main barrier against external elements. As the largest organ, it makes up around 16% of the body's length, typically covering an area between 1.5 and 2.0 square meters and representing roughly 6-10% of total body weight. Composed of multiple cellular layers, human skin can be classified into two main types: hairless and hair-bearing skin. Hair-bearing skin includes both hair follicles and sebaceous glands.

2.1. Layers of skin

2.1.1Epidermis

The epidermis is the skin's outermost layer, functioning as a vital protective barrier. It consists of stratified epithelial cells and keratinocytes that actively multiply in the suprabasal area, with basal layers showing differentiation. The thickness of the epidermis varies, with regions like the palms and soles reaching about 0.8 mm. It is composed of several layers of epithelial cells, and the lower layers are commonly known as the viable epidermis. Keratinocytes are the dominant cells in this layer.

2.1.2 Dermis

Located below the epidermis, the dermis is a complex, fibro-elastic layer that provides the skin with structural strength. It contains an extensive network of nerves and blood vessels. Discomfort during parenteral drug administration can result from possible irritation to nerve endings within this layer.

2.1.3 Hypodermis

The hypodermis, or subcutaneous fat layer, supports the epidermis and dermis by storing fat, regulating temperature, and providing cushioning. It contains significant blood vessels and nerves extending to the skin and may house sensory pressure receptors. For transdermal drug delivery, medications must penetrate the epidermis, dermis, and hypodermis to enter the bloodstream, while topical applications focus on permeating the stratum corneum for retention in the skin layers.

- **Skin and drug permeation**

Understanding Transdermal Drug Delivery Systems (TDDS) requires examining the skin's structure and biochemistry, as these factors influence its barrier properties and the rate of drug absorption. Covering roughly 2 square meters in an average adult, the skin is one of the largest organs and receives about one-third of the body's blood flow. The epidermis, the outermost skin layer, is about 150 micrometers thick, formed through the continuous movement of basal epithelial cells migrating to the surface as they differentiate. Below the epidermis, other layers include the stratum lucidum, stratum granulosum, stratum spinosum, and stratum germinativum, known collectively as the viable epidermis.

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The dermis lies beneath the epidermis, acting as the connective tissue foundation and originating from the mesoderm. It consists of a dense network of connective tissues, primarily collagen fibers, along with some elastic tissue in its upper layers. The dermis also houses blood vessels, lymphatic vessels, nerves, as well as structures like hair follicles, sweat glands, and sebaceous glands.

3.1. Functions of skin

- Acts as a protective shield against physical, mechanical, and thermal damage, as well as against harmful substances.
- Helps retain moisture to keep the skin hydrated.
- Minimizes the harmful effects of UV radiation from sunlight.
- Serves as a sensory organ, enabling the sensation of touch and temperature changes.
- Aids in temperature regulation by releasing sweat to cool the body as needed.
- Functions as part of the immune system, detecting and responding to potential infections.
- Contributes to vitamin D synthesis when exposed to sunlight.

[These diverse functions highlight the skin's essential and adaptable role in the human body.]

3.1.1. Barrier functions of the skin

The outermost layer of the skin, the stratum corneum, is crucial in preserving the skin's barrier function. In this layer, tightly packed and overlapping cells provide a strong defense against bacterial invasion while helping to maintain moisture. The stratum corneum is mainly composed of keratinized dead cells and contains less water than other skin layers. To reinforce this barrier, lipids are released by cells from deeper skin layers to the surface, where they form a sturdy, interlocking network similar to mortar between bricks in a wall.

- **Basic components of TDDs**
- Drug
- Polymer matrix
- Permeation enhancers
- Adhesives
- Backing membrane
- Release Linear [28]

4.1. Drug

- For effective transdermal absorption, drugs must have specific physicochemical properties, such as low irritation potential, molecular weights under 1000 Daltons, low melting points, short half-lives, and a balanced affinity for both lipophilic and hydrophilic environments. Selecting suitable drugs for TDDS is crucial to successful system development[30].

4.1.1 Polymer matrix

Polymers play a vital role in TDDS by controlling the drug's release rate. The polymer matrix can incorporate the drug in a solid or liquid form. In intramuscular drug delivery, biodegradable polymers, either natural or synthetic, are essential for matrix formation, where the drug is dispersed. For targeted injectable delivery, the polymer must be stable and compatible with the drug and other system components, ensuring a safe and controlled release. In TDDS, various polymers are utilized, including:

- Synthetic elastomers: polybutadiene, polyisobutylene, silicone rubber, etc.
- Synthetic polymers: polyvinyl alcohol, polyvinyl chloride, polyethylene, etc.
- Natural polymers: cellulose derivatives, waxes, gums, and eudragits, among others.

4.2. Permeation enhancers

These agents can temporarily modify the structure of the stratum corneum, which enhances drug penetration from the skin into the bloodstream. They work by disrupting the organized lipid layers in the stratum corneum, either by inserting amphiphilic molecules or removing lipids. This temporary change lowers the skin's barrier resistance, promoting better drug absorption.

An ideal permeation enhancer should be Inert, non-toxic, non-allergenic, non-irritating, and function in a one-way manner. It should also be compatible with both the drug and other components in the formulation. The effectiveness of these enhancers depends on the drug type, skin properties, and concentration used. A diffusion cell is used to measure how much drug penetrates the skin. These compounds increase stratum corneum permeability to achieve therapeutic drug levels by directly interacting with the skin barrier.

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4.3. Adhesives

Unlike multi-layer or single-layer adhesive systems, the reservoir transdermal system has a unique drug reservoir within a compartment made from a drug-impermeable metallic laminate, featuring a rate-controlling membrane on one side. To keep layers separated, a specialized adhesive, such as polyacrylates, polyisobutylenes, or silicone derivatives, is used to secure the system in place.

4.4. Backing membrane

The backing layer in a transdermal patch serves to protect the system from external factors. This layer is impermeable to both drugs and penetration enhancers, providing structural support for the patch and shielding the drug reservoir from environmental exposure. Common backing materials include polyester, aluminized polyethylene terephthalate, and siliconized polyethylene terephthalate. These backing laminates are crucial for supporting the patch, preventing drug loss through the top layer, and allowing for printing on the patch.

4.5. Release Linear

To protect the transdermal patch during storage, a liner is placed over it and removed just before application. While not an integral part of the drug delivery system, this liner serves as primary packaging. Common materials for release liners in transdermal systems include polyester foil and metalized laminate.

- **Transdermal systems can be divided into two layer systems:**
- The single-layer drug in adhesive
- The multi-layer drug in adhesive

5.1. Single Layer Drug in Adhesive

In the Single-Layer Drug-in-Adhesive system, the drug is contained in a single layer that adheres directly to the skin. A typical transdermal patch has three main layers: the backing membrane, an adhesive layer with the drug, and a protective liner. The adhesive layer lies between the temporary liner and the backing layer, ensuring proper adhesion to the skin.

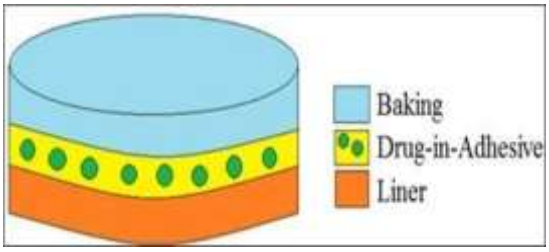

Figure 1 Single layer drug in adhesive [39]

5.2. Multi-layer drug in adhesive

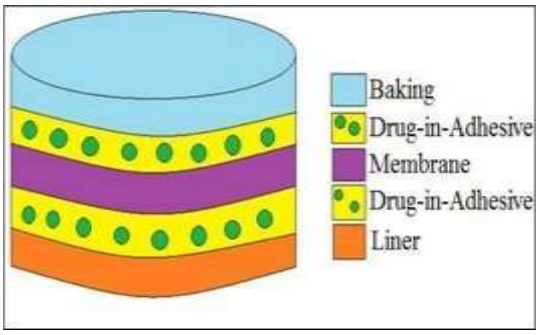

Figure 2 Multi-layer drug in adhesive [39]

Similar to the single-layer system, the multi-layer drug-in-adhesive patch delivers the drug through both adhesive layers. It includes one layer for immediate drug release and another layer for sustained release from a reservoir. The multi-layer system differs by having an additional drug-in-adhesive layer, often separated by a membrane. Known as the Multi-Layer Drug-in-Adhesive system, it also includes a permanent backing layer and a removable liner.

5.2.1Reservoir

In transdermal drug delivery, reservoir systems are characterized by a compartment that holds a drug solution or suspension, separated from the release liner by a semi-permeable membrane and adhesive layer. The adhesive, which secures the patch to the skin, may form a continuous layer between the membrane and the liner or be arranged concentrically around the membrane.

A key feature of reservoir systems is their ability to provide zero-order drug release, delivering the drug at a steady and predictable rate throughout the treatment period.

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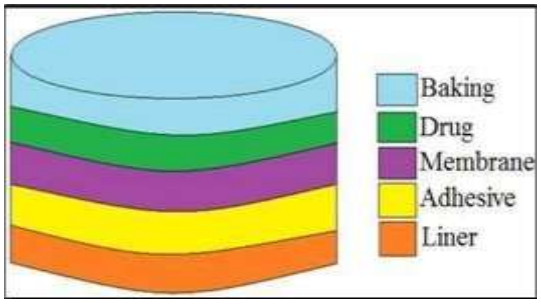

Figure 3 Reservoir [39]

5.2.2 Matrix

A basic transdermal patch design includes three main elements: the drug, an adhesive, and a structural support layer for the patch. In this setup, the drug is embedded within a polymer matrix, simplifying the manufacturing process. Unlike reservoir systems, this design does not include a rate-controlling membrane. However, these patches may be less flexible compared to reservoir systems. In this design, the drug release rate is mainly governed by the permeability of the skin.

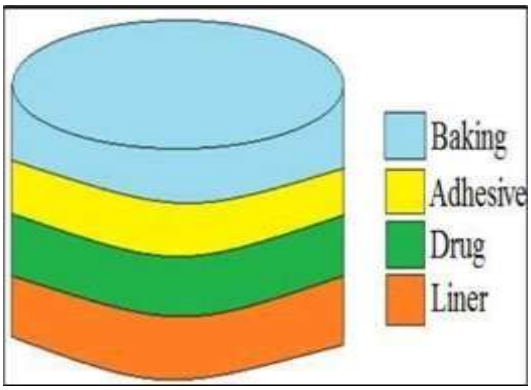

Figure 4 Matrix **[39]**

5.3. Route of drug penetration across skin

When a molecule comes into contact with unbroken skin, it encounters various substances such as cellular debris, microorganisms, and sebum. This interaction provides the diffusant with three potential pathways to access viable tissue: it can enter through the hair follicles and their associated sebaceous glands, navigate through sweat ducts, or pass through the intact stratum corneum that separates these skin structures.

5.3.1 Transcellular Route

Drugs that penetrate the skin via the transcellular route move through the corneocytes. These corneocytes, abundant in hydrated keratin, create a water-rich environment that facilitates the passage of hydrophilic drugs. The transcellular pathway requires not only partitioning into and diffusing through the keratin "bricks" but also infiltrating and traversing the intercellular lipids.

5.3.2Intercellular Route

The intercellular route allows drugs to diffuse through a continuous lipid matrix. Solutes navigate through the lipid regions by diffusing between the horny cells of the stratum corneum, the viable cells of the epidermis, and into the dermis.

This pathway presents notable challenges for two primary reasons:

i. According to the "bricks and mortar" model of the stratum corneum, the interlocking structure of the corneocytes creates a complex pathway for drugs to permeate intercellularly, unlike the more straightforward transcellular route.
ii. The intercellular area consists of alternating structured bilayers, meaning a drug must go through repeated cycles of partitioning and diffusing between both aqueous and lipid domains.

This route is generally regarded as the most common for small, uncharged molecules to penetrate the skin.

5.3.3Transappendageal Route

Also known as the "shunt pathway," this route allows drug molecules to pass through hair follicles, travel along the sebaceous pathways of the pilosebaceous apparatus, or use the aqueous pathways of the eccrine sweat glands. However, this transappendageal pathway is considered less significant due to its small surface area, which constitutes less than 0.1% of the overall skin surface.

Kinetics of Transdermal Permeation

A thorough understanding of transdermal dynamics is essential for the effective development of transdermal devices. This understanding encompasses several critical components:

- "Horny Layer Absorption": This term refers to the uptake of drugs through the stratum corneum, which is the outermost skin layer.
- "Drug Absorption Across Skin Layers": This involves the process of drug molecules passing through various skin layers, such as the epidermis and dermis, to enter the bloodstream.

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- "Absorption in the Epidermal-Dermal Papillae": This focuses on how drugs are absorbed within structures called epidermal-dermal papillae, found within the epidermis where it interfaces with the dermis.

Each of these elements plays a vital role in the overall process of transdermal drug delivery.

1. Factor affecting transdermal permeability Physicochemical Factors

- Partition coefficient [51]

For effective transdermal permeability, a lipid/water partition coefficient of 1 or higher is generally required. This coefficient indicates how a drug partitions between lipid (fat) and water, with values above 1 suggesting a greater affinity for lipid environments, which is crucial for absorption through the skin.

It is important to recognize that chemical modifications can sometimes change this partition coefficient without substantially impacting the drug's pharmacological activity. This approach can be an advantageous strategy in drug development to improve transdermal delivery while preserving the drug's therapeutic efficacy.

- Skin Hydration

The permeability of the skin rises considerably upon exposure to water. Hydration plays a vital role in enhancing this permeability. As a result, humectants are frequently utilized in transdermal delivery. These substances aid in moisture retention and keep the skin hydrated, which can improve the absorption of drugs and other compounds through the skin.

- Temperature and pH

Temperature significantly influences the permeability of drugs through the skin. When temperatures increase, drug permeability can rise sharply, sometimes by tenfold or more. On the other hand, a decrease in temperature leads to a reduced diffusion coefficient for drugs within the skin, which can impact the rate at which drugs are absorbed through the skin.[52]

- Penetrant concentration

In transport involving membranes, it is commonly noted that a rise in the concentration of a dissolved drug results in a corresponding increase in flux, which refers to the rate of drug movement across the membrane. Furthermore, when the concentration of the drug exceeds its solubility threshold, any surplus solid drug can serve as a reservoir. This reservoir effect aids in maintaining a stable drug concentration at the membrane interface over a prolonged period, facilitating sustained release of the drug. [53]

- Molecular Weight

The process of percutaneous absorption, where substances move through the skin, typically shows an inverse relationship with the drug's molecular weight. Smaller molecules are usually absorbed more easily. In a passive diffusion system for transdermal drug delivery, drugs with a molecular weight of less than 500 Daltons are generally preferred. Nonetheless, the permeation rate can be improved by utilizing different penetration enhancers that assist larger molecules or those with less ideal characteristics in traversing the skin. [54]

5.4. Biological factors [55]

5.4.1 Skin condition

The skin functions as a natural defense against numerous substances; however, certain agents, including acids and alkalis, can infiltrate the skin, especially if they are corrosive or can damage skin tissue. Solvents like methanol and chloroform are recognized for their ability to strip away the skin's lipid layer, leading to the formation of tiny openings that may facilitate the absorption of other substances. These interactions underscore the necessity of comprehending how different agents affect the skin's barrier properties, particularly in situations involving chemical exposure or transdermal drug delivery.

5.4.2 Skin age

The sensitivity of skin to different substances can indeed differ between individuals and age groups. Typically, the skin of young children and adults tends to be more reactive or vulnerable to certain agents compared to that of older adults. This variation can be attributed to differences in skin thickness, composition, and the effectiveness of natural protective barriers.

Certain substances, such as specific acids, steroids, boric acid, and hexachlorophene, may cause particular side effects or adverse reactions when applied to children's skin. Children's skin is generally more sensitive and can absorb and respond to substances in a way that differs from adult or elderly skin. Consequently, it is crucial to exercise caution and adhere to appropriate guidelines when using these substances on

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children, especially in medical or healthcare situations.

5.5. Different generations of TDDS

There are Four generations of TDDS according to the advancement of the TDDS, which are as follows.

- First Generation
- Second Generation
- Third Generation
- Fourth Generation

5.5.1 First Generation

The first generation of basic transdermal patches began to appear in the early 1970s. Following the initial approval from the U.S. Food and Drug Administration (FDA) for the scopolamine patch intended for motion sickness, around 19 different types of patches have been commercially produced, including those for nicotine, menthol, and estradiol. However, the range of drugs that can be effectively formulated into patches is still limited due to the physiological barriers of the epidermis. Most of the transdermal drugs from this initial generation are highly lipophilic, exhibiting partition coefficients greater than 10^4, having small particle sizes, and molecular weights below 400 Daltons. Research in this period focused on tailoring the physicochemical characteristics of these chemical compounds. Essentially, drugs designed for transdermal delivery were either specifically selected or modified to have a high partition coefficient and a low molecular weight to enhance their ability to diffuse through the skin barrier.

5.5.2 Second Generation

The second generation of Transdermal Drug Delivery Systems (TDDSs) was created to enhance the ability to deliver small molecule drugs through the skin. These systems are based on two key principles:

- Modification of Drug Properties: Drugs are altered to exhibit optimal characteristics, such as an appropriate logarithm of the partition coefficient (log P), which aids in their absorption through the skin.
- Structural Changes in the Stratum Corneum (SC): The structure of the SC is modified or pore channels are created within it using various physicochemical techniques. These changes create an additional driving force for the drug to penetrate the skin, thereby improving the efficiency of transdermal drug delivery.

Although second-generation TDDSs established a foundation for enhancing drug delivery efficiency, they encountered certain limitations. A major challenge was achieving an optimal balance between maximizing drug absorption through the SC while safeguarding the underlying tissues from potential harm. This challenge paved the way for the development of third-generation TDDSs, which likely sought to resolve these issues and further enhance transdermal drug delivery systems. [57]

5.5.3 Third Generation

The third generation of Transdermal Drug Delivery Systems (TDDS) is distinguished by its minimally invasive techniques that involve disrupting the stratum corneum (SC) to enable the absorption of larger molecule drugs and even vaccines through the skin. Two primary methods used in this generation of TDDS are electroporation and microneedling.[58, 59].

Electroporation employs electric pulses to temporarily disrupt the structure of the SC, creating transient pores. This approach enhances the effectiveness of transdermal drug distribution while protecting deeper tissues. In contrast, microneedling utilizes tiny needles to form microchannels in the SC, which aids in the delivery of drugs into the skin. These techniques provide the opportunity to administer a broader array of medications and vaccines through the skin while reducing invasiveness and ensuring the safety of underlying tissues. [60]

5.5.4 Fourth Generation

Personalized therapy marks a notable shift from traditional medical approaches as it customizes treatment based on each person's specific pathophysiological conditions. Implementing personalized therapy requires careful management of the dosage given, informed by real-time tracking of the patient's physiological parameters. This method allows for a tailored assessment of disease progression and drug efficacy.

In response to the increasing demand for individualized treatments, advanced transdermal delivery systems augmented by soft bioelectronics have emerged as a promising avenue for future drug delivery techniques. These systems can offer more precise and flexible drug administration, effectively addressing the unique requirements of

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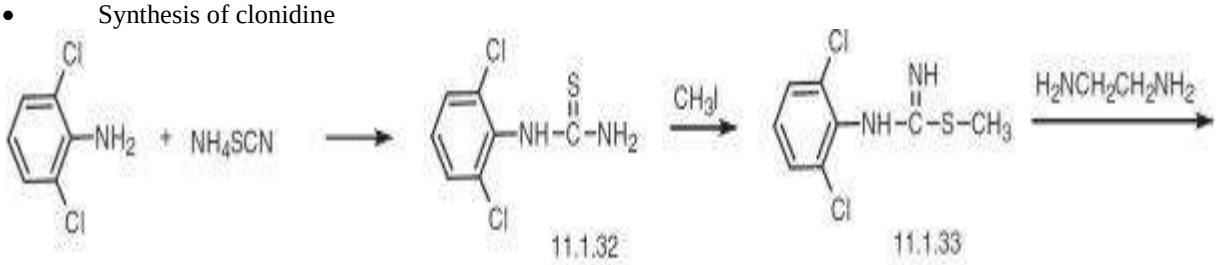
each patient. [61]

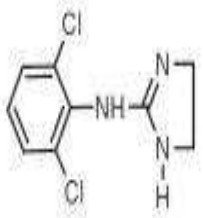
- Drug uesd as an antihpertensive patches
- Clonidine: Clonidine is a centrally acting alpha adrenergic agonist and antihypertensive drug that works by reducing sympathetic outflow from the central nervous system. Clonidine ia an antihypertensive medication that can be administered a transdermal patches .the clonidine patch is a desingned for sustained controlled releses of the drug over a period of 7 days providing a steady dose of the medication and reducing the need for oral dosing

- Mechanism of Action Clonidine:

Clonidine has an alpha-antagonist effect in the posterior hypothalamus and medulla. The final response is reduced sympathetic outflow from the central nervous system (CNS), which clinically causes a decrease in arterial blood press.

- Synthesis of clonidine





11.1.34

- Structure of clonidine

Uses of chlonidine:

- It is used an an adjunet for treating hpertension
- For managing severe cancer pain not relieve by opiate analgesic
- For diagnosing pheochronacytoma in hyepertensive paitent

Common Adverse Drug Reactions:

1. **Sedation and Drowsiness**: Clonidine can cause central nervous system (CNS) depression, leading to drowsiness, sedation, or fatigue. This is especially common when starting the medication or adjusting the dose.
2. **Dry Mouth (Xerostomia)**: A frequent side effect that may occur, leading to discomfort and difficulty swallowing.
3. **Hypotension**: Clonidine's primary mechanism of action is to lower blood pressure, which can lead to excessive hypotension (low blood pressure), especially when starting the medication or after dose increases.
4. **Bradycardia**: Clonidine can decrease heart rate (bradycardia), which may be symptomatic

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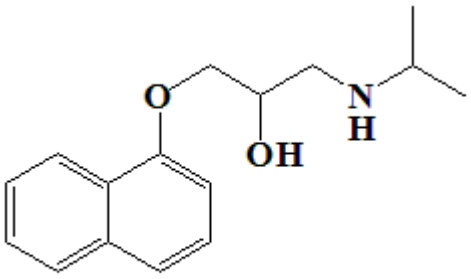
in some patients, especially those with pre-existing heart conditions.

5. **Dizziness**: Dizziness, lightheadedness, or even fainting, particularly when standing up quickly (orthostatic hypotension), can occur due to its blood pressure-lowering effects.
6. **Constipation**: This is a less common side effect but may occur in some individuals.
7. **Headache**: Some patients report headaches, which may occur as part of the medication's systemic effects.

- Propranolol: Propranolol is a medication that belongs to a class of drugs called **beta-blockers**. It works by blocking the effects of certain natural substances in the body, such as adrenaline (epinephrine), on beta receptors in the heart and blood vessels. This helps to lower blood pressure, reduce heart rate, and decrease the workload on the heart. Propranolol is used to treat various conditions, including:

1. **Hypertension (high blood pressure)**
2. **Angina (chest pain)**
3. **Arrhythmias (irregular heartbeats)**
4. **Heart attack recovery**
5. **Migraine prevention**
6. **Anxiety (especially performance anxiety or stage fright)**
7. **Tremors**
8. **Thyroid storm (in cases of hyperthyroidism)**

Structure of propranolol



propanolol

- Adverse drug reaction of propranolol:

Serious skin reactions can occur with this medicine. Check with your doctor right away if you have blistering, peeling, or loose skin, red skin lesions, severe acne or skin rash, sores or ulcers on the skin, or fever or chills while you are using this medicine. Propranolol may cause heart failure in some patients

Mechanism of action:
Propranolol
Inhibits vasomotor conduction
Decrease svmpathetic dischrarge
Vasodilation
Decreases blood pressure

Side effects of propranolol:

The main side effect of propranolol are feeling dizzy or tried cold hand or feet .difficulties sleeping and nightmares.

Uses of propranolol
Propranolol is used alone or in combination with other medication to treat high blood pressure.

II. CONCLUSION

TDDS are topically administration of medicaments through the skin for systemic effects at a predetermined and controlled rate in the form of transdermal patches. Transdermal drug delivery of antihypertensive drugs is able to provide optimum of drug to control the disease condition along with minimum side effects. This review on different antihypertensive drugs showed that, by delivering drug through this route improves bioavaibility a well as patient compliance. This can also lead to cost effectiveness of a healthcare for the long term management of hypertension. But the main limitation is that, the drug should possess certain specific physicochemical properties which should be suited to permeate through the skin, therefore all antihypertensive drugs cannot be given by this route. Transdermal drugs market is growing and there is a prospect of higher growth in this market over the next several years. Transdermal delivery of antihypertensive drugs is expected to have a profound impact on patient care.

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