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Formulation and evaluation of transdermal patch of Etodolac

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ABSTRACT

A transdermal patch is an adhesive medication that goes through your skin and into the bloodstream. These days, transdermal patches are widely used as delivery systems for topical, transdermal, and cosmetic products.Transdermal patches work in different ways, as does the active medication ingredient's passage through the skin from the patch to the circulatory system.Etodolac transdermal patch acts as a type of controlled drug delivery system used to boost the efficiency,compliance and convenient to patients.Transdermal patches are novel methods to deliver a drug into skin at a controlled rate while maintaining the therapeutic concentration. In transdermal patches drug is administered via skin which is an integral part of transdermal drug delivery system. Skin serves numerous purposes. Along with offering protection from many types of stress, such as thermal, chemical, and UV radiation, it also acts as a barrier against infections and water loss. Through a variety of nerve endings, the skin communicates with our surroundings, controls body temperature, improves metabolic processes, and synthesizes vitamin D.The skin has two main layers: the epidermis, which covers our body and prevents water loss, and the dermis, which has many glands, blood vessels, and receptors. Skin plays an important role transdermal drug delivery system such as barrier and drug absorption.This etodolac transdermal patch acts as a very useful patch because the drug layer constitutes as a rate-controlling membrane for effective and controlled drug release. This review can acts as the base for future research on this topic.

Keywords: *Controlled drug delivery system, Etoldolac, rate controlling membrane, skin, transdermal patch.*

1. INTRODUCTION

Controlled drug delivery system

In addition to reducing toxicity and improving patient care, the quickly evolving field of controlled drug delivery technology also boosts efficiency, compliance, and convenience—all of which are beneficial to human health. Site-targeting, feedback-regulated, activation-modulated, and rate-preprogrammed are the four main types of controlled drug delivery systems. Subcutaneous implants, ocular inserts, intrauterine delivery, and transdermal administration are new methods for administering drugs via the skin at a precise rate while preserving therapeutic concentration. Some of the applications for these systems are shingles pain, angina, motion sickness, estrogen, and smoking cessation..(Gowdhaman *et al* ., 2015)

Types of controlled drug delivery system

Targeted drug delivery, pH-sensitive, temperature-sensitive, diffusion-controlled, dissolution-controlled, osmotic-controlled, activation-modulated, magnetic and ultrasound-triggered, feedback-regulated, and biosensor-based insulin pumps are examples of controlled drug delivery systems.

Benefits of CDDS system

1. improves patient adherence, reduces dosing frequency, and keeps blood medication levels constant.
2. Lessens drug toxicity and side effects

3. Enhances bioavailability and treatment efficacy.

Limitations of CDDS

Controlled-release systems, or CDDS, have a number of drawbacks, such as high development costs because of sophisticated technology and long-term research, complicated formulation and manufacturing because of sophisticated drug carriers, limitations on drug properties, patient variability, the possibility of dose dumping, limited use in emergency situations, and sensitivity to the environment and storage. Due to these features, CDDS may need to be stored according to stringent rules because of the possibility of deterioration under specific conditions, and it is not appropriate for conditions like extreme pain or cardiac arrest.

Uses

- Management of chronic illnesses like cancer, diabetes, and high blood pressure
- Managed pain
- Neurological conditions (such as Alzheimer's and Parkinson's)(Adepu & Ramakrishna, 2021)

Transdermal patch

To put it simply, a transdermal patch is an adhesive medication that goes through your skin and into your bloodstream. These days, transdermal patches are widely used as delivery systems for topical, transdermal, and cosmetic products. The progress in skin science, technology, and knowledge brought about by clinical observation, trial and error, and evidence-based study dating back to the oldest human records is largely responsible for these patches.(Pastore *et al* ., 2015)

Transdermal drug delivery system

Although administering medications transdermally has greatly enhanced medical practice, it has not yet fully realized its potential as an alternative to oral delivery and hypodermic injections. The use of first-generation transdermal delivery methods in clinical settings to distribute small, lipophilic, low-dose drugs has been increasing significantly.. (Alam *et al* ., 2013)Iontophoresis, chemical enhancers, and noncavitational ultrasound are examples of second-generation delivery technologies that have been used to generate clinical items; the latter's real-time distribution rate control adds capability. In order to target the stratum corneum, the skin's protective layer, third-generation delivery techniques employ cavitational ultrasound, thermal ablation, microneedles, microdermabrasion, and electroporation. Current clinical trials are being carried out with microneedles and thermal ablation for the delivery of macromolecules and vaccinations, such as insulin, parathyroid hormone, and influenza vaccine. (Prausnitz & Langer, 2008)

Advantages of transdermal patch delivery system

1. Sustained Release: TDDSs minimize fluctuations in blood drug levels by administering a dose of medication in a consistent manner over an extended distance. For drugs that require continuous therapeutic effects, this is beneficial.
2. Patient Compliance: The convenience of wearing a patch can help patients stick to treatment plans, especially for chronic conditions.
3. Decreased Side Effects: By skipping the liver and digestive tract, TDDSs can reduce the risk of gastrointestinal side effects associated with oral drugs and diminish first-pass metabolism, which can make some pharmaceuticals inactive.
4. Non-Invasive nature: injectable or oral medications can be easily and non-invasively replaced with TDDSs.
5. Enhanced Bioavailability: Compared to oral treatment, transdermal administration can boost the bioavailability of numerous drugs because it avoids the liver's first-pass processing.(Petrofsky *et al* ., 2014)

Disadvantages of transdermal drug delivery system

1. Limited Drug Suitability: There are just a few drugs that can be effectively administered through the skin. Certain characteristics, such as high potency, low molecular weight, and good skin permeability, are required of these drugs.
2. Allergies and Skin Irritation: Some persons may experience skin irritation or allergic responses at the application site.
3. Drug Interactions: Topical medications applied to the same skin area may have the potential to interact with one another.
4. Sensitivity to temperature: Changes in temperature may affect how quickly medications are released from specific patches.

5. The amount of medication that can be applied via a patch is limited by the skin's capacity to absorb it.
6. Patient-related factors: One's degree of exercise, skin health, and hair development can all affect how well the medication is absorbed from the patch.(Rastogi & Yadav, 2012)

Skin

Skin serves numerous purposes. Along with offering protection from many types of stress, such as thermal, chemical, and UV radiation, it also acts as a barrier against infections and water loss. Through a variety of nerve endings, the skin communicates with our surroundings, controls body temperature, improves metabolic processes, and synthesizes vitamin D.(I.V. Yannas, 2001)

The skin has two main layers: the epidermis, which covers our body and prevents water loss, and the dermis, which has many glands, blood vessels, and receptors. The skin has the largest surface area in the human body.(Venus, 2011)The three layers that comprise the skin are the epidermis, dermis, and subcutaneous tissue.(Kanitakis, 2002)The outermost layer, the epidermis, is composed of a specific cell type known as keratinocytes, which are in charge of producing keratin, a long, thread-like protein with defensive qualities. The middle layer, or dermis, is basically composed of collagen, a fibrillar structural protein. The panniculus, or subcutaneous tissue, which is composed of microscopic lobes of lipocytes—fat cells—is where the dermis lies. The thicknesses of these layers vary greatly depending on the region and the anatomy of the body. For example, the eyelid's epidermal layer is the thinnest, measuring less than 0.1 mm, while the soles of the feet and palms are the thickest, measuring about 1.5 mm. The dermis of the back is between 30 and 40 times thicker than the covering epidermis. (James, 2006)

Role of skin in TDDS

Barrier: The skin's primary function is to act as a barrier. The body is protected from external elements such as UV radiation, pollution, and infections by it.

Drug distribution, however, is hampered by its barrier function. The stratum corneum, the outermost layer of the skin, is relatively impenetrable to many things because it is composed of dead cells and that are packed closely together. (Guy 2024)

Drug Absorption: Despite its barrier function, the skin allows the absorption of certain drugs. To ensure a good transdermal distribution, this challenge must be overcome. In order to reach the dermal blood vessels underneath, medication molecules need to go through the stratum corneum. (Alkilaniet,al, 2015)

Elements That Affect Absorption

A. Skin Properties: Skin thickness, moisture content, and overall health can all have a significant effect on drug absorption.
B. Features of the Drug: The drug molecule's size, charge, and lipophilicity (fat solubility) all affect its capacityto penetrate the skin.
C. Patch Design The adhesive, drug concentration, and rate-controlling membrane that make up the patch are important components that affect drug release and absorption. (Souto et.al., 2022)

Routes for Drug Penetration

A. Transcellular Pathway: Drug molecules pass directly through the cells of the stratum corneum. The intercellular pathway connects the cells of the stratum corneum, where drug molecules travel.
B. Appendageal Pathway: Drug molecules enter through hair follicles and sweat glands. (Souto et.al., 2022) (Tadhi*et al* , 2021)

Formulation Elements

a. Design of the TDDS: The kind of TDDS (reservoir, matrix, etc.) affects the drug release profile. The TDDS's composition, particularly the polymers used, affects drug dispersion.
b. Penetration Enhancers: These substances are used to increase the permeability of the skin, thus their choice and concentration are very important. The effectiveness of penetration enhancers depends on the drug and skin type.
c. Properties of the Vehicle/Matrix: The viscosity and pH of the matrix or vehicle may affect drug release and skin penetration.
d. The use of nanocarriers, such as cubosomes or nanoemulsions, requires consideration of factors including zeta potential and particle size.

Factors affecting permeation and penetration in the skin:(Vaseem *et al* ., 2024)

1. Physiological Factors

- **Skin Thickness** (Varies by body site)
- **Stratum Corneum Hydration** (Higher hydration increases permeability)
- **Age of the Skin** (Elderly and neonatal skin differ in permeability)
- **Blood Flow** (Affects drug absorption)
- **Skin Temperature** (Higher temperature increases diffusion)

1. **Physicochemical Properties of Drug**

- **Molecular Size & Weight** (Smaller molecules penetrate better)
- **Lipophilicity/Hydrophilicity** (Balance needed for penetration)
- **Ionization State** (Non-ionized drugs have better permeability)
- **Drug Solubility** (Higher solubility enhances absorption)

2. **Formulation Factors**

- **Drug Concentration** (Higher concentration increases permeation)
- **Vehicle/Base Used** (Lipophilic or hydrophilic nature affects penetration)
- **Penetration Enhancers** (e.g., surfactants, terpenes, ethanol)
- **Polymer Matrix or Reservoir Type** (Affects release rate)

3. **Application Conditions**

- **Application Site** (Forearm, back, or behind the ear may have different permeabilities)
- **Duration of Application** (Longer exposure increases absorption)
- **Occlusion (Covering the Patch)** (Prevents water loss, enhances permeability)

Components of Drug Delivery System

Medication(API, or active pharmaceutical ingredient)

- The medication should have a suitable lipophilicity and molecular weight (preferably between 100 and 500 Da).
- It must have a short biological half-life and be released under carefully monitored circumstances.

Fentanyl, nicotine, nitroglycerin, and estrogen are a few examples.

Reservoir or Polymer Matrix

- Controls release and transports drugs.
- Common polymers include:
- Natural: Gelatin, chitosan, and fiber-derived cellulose.

They are synthetic: polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG), and polyvinyl alcohol (PVA).

Enhancers of Permeation

- Improve drug absorption by changing the properties of the epidermal barrier.

Chemical boosters include alcohol, propylene glycol, oleic acid, and dimethyl sulfoxide (DMSO).

Microneedles, ultrasound (sonophoresis), and iontophoresis are examples of physical enhancers.

Backing Layer

Polyethylene, polypropylene, and polyester film make up the backing layer, which protects the patch from the weather and prevents medicine loss.

Adhesive Layer

Guarantees that the patch adheres to the skin properly.

may be acrylic-based adhesives or pressure-sensitive adhesives (PSAs) such as polyisobutylene.

Release Liner

Before applying, a protective covering was taken off.

composed of materials such as polyester film coated with silicone.

Rate Controlling Membrane (For Reservoir Type Systems)

Controls the flow of medication to the skin from the reservoir.

Ethylene Vinyl Acetate (EVA) and silicone membranes are common materials. (Parivesh *et al* ., 2010)

Different types of transdermal patches

Transdermal patches can be grouped according to their structure and medication release methods. In general, they fall into two categories: matrix patches and reservoir patches. Adhesive-controlled and membrane-controlled reservoir patches are the two varieties. Conversely, matrix patches consist of drug-in-adhesive and adhesive-in-matrix techniques.

Transdermal patches are classified as either passive or active systems based on how the drug is released. Passive drug delivery techniques that use diffusion include matrix and reservoir systems. Iontophoresis, sonophoresis, microneedles, and electroporation, on the other hand, are examples of active systems that use external pressures to enhance medication penetration.

Transdermal patches come in single-layer or multi-layer structural variations. Drug-in-adhesive and adhesive-in-matrix patches are the two forms of single-layer patches. A drug layer with a rate-controlling membrane to effectively control drug release, or a combination of drug-in-matrix systems, may be present in multi-layer patches. (Adhyapak & Desai, 2016)

Innovation in transdermal patch

1. Microneedle Patches (MNPs): These patches use arrays of tiny needles to painlessly pierce the epidermis, spreading both large and small molecules efficiently. Vaccine administration and cosmetic operations are only two of the many applications for which MNPs have been studied. They are less painful and offer faster drug absorption than traditional methods.
2. Smart Insulin Patches: Designed to aid diabetics, these patches include glucose-responsive microneedles loaded with insulin. To control blood sugar, the patch releases insulin when it detects rising blood glucose levels, possibly eliminating the need for repeated injections. In animal models, they have demonstrated efficacy, and human clinical trials are planned.
3. Prostate Cancer Hormone Delivery Patches: As an alternative to traditional hormone therapies for prostate cancer, new studies have investigated the use of estradiol-containing skin patches. With fewer side effects like hot flashes and high blood pressure, these patches are meant to provide effective androgen deprivation therapy in contrast to conventional treatments.
4. Vitamin patches: Transdermal vitamin patches have gained popularity as an alternative to oral supplements for those who have difficulty swallowing tablets or who prefer to get their nutrients in another way. However, there is disagreement among medical professionals on their benefits; some study indicates that users have limitations, in which case their efficacy is called into question.
5. Technology for TEPI Patches: This technology, developed by Medherant Ltd., creates patches that may transdermally administer drugs using polymer chemistry and bioadhesives. The TEPI patch aims to improve patient compliance and offer controlled dosing in preparation for the introduction of painkillers that use nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen. (Tiwaryet.al., 2008) (Guy et.al.,1996)

2. MATERIAL AND METHODS

Materials used

1. **Active Pharmaceutical Ingredient (API):**

- **Etodolac** – A non-steroidal anti-inflammatory drug (NSAID) used for pain and inflammation.

2. **Polymers (Film-forming agents):**

Used to form the matrix that controls drug release:

- **Hydroxypropyl methylcellulose (HPMC)**
- **Polyvinylpyrrolidone (PVP)**
- **Eudragit® (e.g., RL100, RS100)**
- **Ethyl cellulose**
- **Carbopol***(optional)*

3. **Plasticizers:**

Improve flexibility, durability, and film-forming properties:

- **Polyethylene glycol 400 (PEG 400)**
- **Glycerin**
- **Dibutyl phthalate (DBP)**
- **Propylene glycol***(optional)*

4. **Solvents:**

Used to dissolve the drug and polymers:

- **Ethanol**
- **Methanol**
- **Chloroform**
- **Acetone***(optional, depending on compatibility)*

5. **Penetration Enhancers***(optional but recommended for better skin permeability)*:

- **Oleic acid**
- **Isopropyl myristate (IPM)**
- **Dimethyl sulfoxide (DMSO)**
- **Tween 80***(non-ionic surfactant)*

6. **Backing Layer Materials:**

Supports the patch and prevents drug loss:

- **Aluminum foil**
- **Polyester film (PET)**
- **Polyethylene film**

7. **Miscellaneous:**

- **Distilled water***(for aqueous polymer solutions, if needed)*
- **Teflon/glass plate** – Used as the casting surface
- **Airtight containers** – For storage and to prevent moisture uptake

Mechanism of preparation of etodolac transdermal patch

Transdermal patches work in different ways, as does the active medication ingredient's passage through the skin from the patch to the circulatory system. The physicochemical characteristics of a systemically active medicine must facilitate its absorption through the skin and entry into the microcirculation in order for it to reach the target region.

The mechanism of preparation of an etodolac transdermal patch involves incorporating the drug into a polymeric matrix that allows for controlled release through the skin. The preparation typically follows solvent casting or dispersion methods, depending on the materials used.

Mechanism of Preparation (Step-by-step - Solvent Casting Method)

1. ***Selection of Polymers and Plasticizers***

- **Polymers** (e.g., HPMC, PVP, Eudragit, or ethyl cellulose) form the matrix of the patch.
- **Plasticizers** (e.g., PEG 400, glycerin, dibutyl phthalate) improve flexibility and film-forming properties.

2. ***Solubilization of Etodolac***

- Etodolac is dissolved or dispersed in a suitable solvent like **ethanol**, **methanol**, or **chloroform**, depending on its solubility.

3. ***Polymer Solution Preparation***

- The chosen polymer(s) are dissolved in the same or a compatible solvent to form a uniform solution.

4. ***Mixing***

- The drug solution is **added slowly** to the polymeric solution with continuous stirring.
- Plasticizer is added during mixing to ensure even distribution.

5. ***Casting***

- The mixture is poured onto a **flat, leveled surface** (e.g., a glass or Teflon plate) using a **film applicator**.
- The casting area is typically controlled to maintain **uniform thickness**.

6. ***Drying***

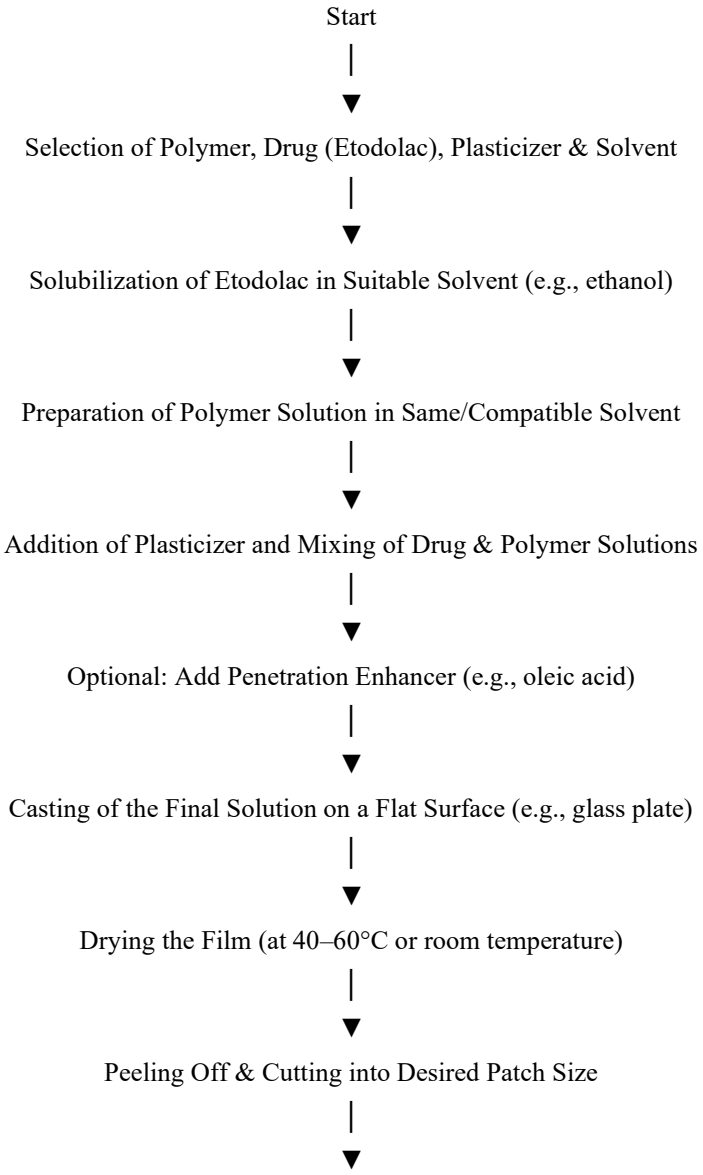
- The solvent is evaporated under **controlled temperature (e.g., 40–60°C)** in an oven or at room temperature.
- This forms a **dry film** containing etodolac embedded in the polymer matrix.

7. ***Cutting and Backing***

- The dried patch is cut into desired sizes (e.g., 2×2 cm).
- A **backing membrane** (like aluminum foil or polyester film) is applied to support the patch and prevent drug loss.

8. ***Storage***

- Patches are stored in **airtight containers** to avoid moisture uptake and degradation.



Application of Backing Layer (e.g., aluminum foil)

▼

Packaging & Storage (airtight container, low humidity)

▼

End

3. RESULTS

The etodolac transdermal patches were successfully prepared using the solvent casting method. The following observations and evaluations were recorded:

1. ***Physical Appearance and Uniformity***

- The patches were **transparent to slightly opaque**, smooth, and **flexible** with **no cracks or air bubbles**.
- All formulations demonstrated **uniform drug distribution** across the surface.

2. ***Patch Thickness***

- The average thickness of the patches was measured using a digital micrometer.
- **Thickness range**: 0.22 mm – 0.30 mm
- The thickness remained **uniform** across different areas of the patch (±0.02 mm variation), indicating consistent film casting.

3. ***Weight Variation***

- Each 2×2 cm patch was weighed.
- **Average weight**: 110 mg – 130 mg
- The variation between patches was within acceptable limits (±5%), showing reproducibility of the method.

4. ***Folding Endurance***

- The patches were repeatedly folded at the same spot until breakage.
- All patches withstood **more than 250 folds**, confirming **good mechanical strength and flexibility**.

5. ***Drug Content Uniformity***

- The drug content was determined by dissolving known patch portions in a suitable solvent (e.g., ethanol), followed by spectrophotometric analysis.
- **Etodolac content** ranged from **96.5% to 101.2%** of the theoretical value, indicating **high uniformity and drug loading efficiency**.

6. ***Moisture Content and Moisture Uptake***

- Moisture content: **2.1% – 4.3%**
- Moisture uptake (at 75% RH): **3.5% – 6.8%**
- The low moisture uptake suggested **good stability and minimal risk of microbial contamination or film degradation**.

7. ***In Vitro Drug Release Study***

- The drug release was studied using Franz diffusion cells with phosphate buffer (pH 7.4).
- **Cumulative release over 24 hours** ranged from **70% to 92%**, depending on the polymer type and concentration.
- The release pattern followed **sustained-release kinetics**, best fitting the **Higuchi model**, suggesting diffusion-controlled drug release.

8. ***Skin Permeation Test (Optional Result if Conducted)***

- Ex vivo permeation through rat or pig skin showed **continuous drug flux** for 24 hours.

- **Steady-state flux (Jss)**: ~18–24 µg/cm²/h (varied slightly by formulation).

4. CONCLUSION

Transdermal patches provide a controlled and sustained release of medication, helping to maintain consistent blood drug levels and minimize fluctuations. This is especially advantageous for drugs like **etodolac**, which require continuous therapeutic action for the management of chronic pain and inflammation. By delivering etodolac steadily over an extended period, transdermal patches can improve therapeutic efficacy and reduce dosing frequency. This method of drug delivery enhances patient compliance, particularly in long-term treatment plans.

Transdermal patch systems are commonly classified into two main types: **drug-in-adhesive** and **adhesive-in-matrix** designs. Additionally, more complex configurations may include a **drug reservoir layer with a rate-controlling membrane**, or a **drug-in-matrix system** that allows for regulated release through diffusion. Etodolac can be incorporated into these systems effectively, depending on the desired release profile and therapeutic needs.

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