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Herbal Transdermal Patches for Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that primarily affects the joints, leading to pain, swelling, and eventual joint destruction. Conventional treatments, including non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying anti rheumatic drugs (DMARDs), often come with significant side effects and limited long-term efficacy. This study aims to develop and evaluate an herbal transdermal patch as a novel therapeutic approach for RA, leveraging the anti-inflammatory and analgesic properties of selected herbal extracts. The research involves a systematic approach, beginning with an extensive review of literature to identify herbs with established therapeutic benefits for RA. Key herbal extracts were selected based on their pharmacological profiles, historical use, and minimal side effects. The transdermal patch formulation was optimized through a series of experiments, focusing on achieving controlled and sustained release of active compounds. Physicochemical characterization of the patches included assessments of thickness, uniformity, moisture content, drug content, and adhesion properties. In vitro studies were conducted to evaluate the drug release profile and skin permeation using Franz diffusion cells and excised animal or human skin. Stability studies ensured the formulation's robustness under various storage conditions. In conclusion, the development of an herbal transdermal patch represents a promising advancement in RA management, combining the benefits of herbal medicine with the advantages of transdermal drug delivery systems. This approach has the potential to improve patient outcomes and quality of life by providing a natural, non-invasive, and effective treatment option for rheumatoid arthritis.

Keywords: Rheumatoid Arthritis; Transdermal Drug; Physicochemical; Lipid Matrix

Abbreviations

RA: Rheumatoid Arthritis; DMARDs: Disease-Modifying Anti Rheumatic Drugs; TDDS: Transdermal Drug Delivery System; SC: Stratum Corneum; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; NPECs: Natural Plant Extracts and Compounds; HLA: Human Leukocyte Antigen; TNF-alpha: Tumor Necrosis Factor-Alpha; P13K: Phosphoinositide-3-kinase; COX: Cyclooxygenase; SOD: Superoxide Dismutase; TLC: Thin-Layer Chromatography; UV: Ultraviolet; HPMC: Hydroxy Propyl Methyl Cellulose; API: Active Pharmaceutical Ingredient.

Introduction

Skin and Drug Permeation

The transdermal drug delivery system (TDDS) is designed to facilitate the systemic absorption of NSAIDs complex multi-layered organ [1].

Approximately one-third of the body's blood supply circulates through the skin [2]. The epidermis, which has a thickness of around 150 µm, originates from a basal layer of actively dividing epithelial cells. This outermost skin layer undergoes a differentiation process, during which cells migrate from the basal layer to the surface [3]. Since the epidermis lacks blood vessels, essential nutrients and waste products diffuse across the dermal-epidermal junction to sustain cellular function [4].

The epidermis consists of five separate layers organized from the deepest to the outermost: the stratum germinativum (basal layer), stratum spinosum (spinous layer), stratum granulosum (granular layer), stratum lucidum, and stratum corneum (SC) [5]. The SC, consisting of non-living cells, functions as the major barrier to transdermal medication penetration. It comprises of 15-20 layers of keratin-rich corneocytes (terminally developed keratinocytes) encased within a lipid matrix [6]. The area of the epidermis underneath the SC is commonly referred to as the viable epidermis because to the presence of live cells. Since the SC acts as the rate-limiting step for most medicinal compounds, knowing its composition and function is critical for improving TDDS formulations [7].

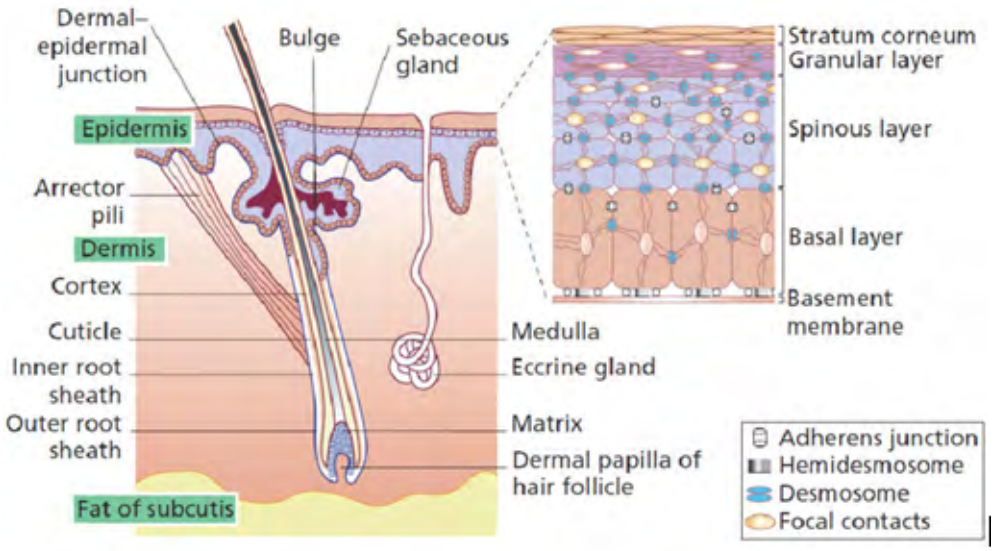


Figure 1: Cross Sectional View of Human Skin with Different layer of cell.

The extracellular matrix lipids of the stratum corneum (SC) exhibit several unique characteristics:
They serve as the sole continuous phase and diffusion pathway extending from the skin surface to the base of the SC [8].

Their composition-comprising ceramides, free fatty acids, and cholesterol-is distinct from other bio membranes, with an absence of phospholipids.

Despite the limited presence of polar bilayer-forming lipids, SC lipids organize into multi-lamellar sheet structures [9]. The predominance of long-chain, saturated hydrocarbon tails promotes a highly ordered, interdigitated arrangement, resulting in gel-phase membrane domains rather than more fluid and permeable liquid crystalline systems [10].

In its dry state, the SC layer measures approximately 10–15 µm in thickness, expanding to 40 µm upon hydration [11]. Structurally, it follows a "bricks and mortar" model, where keratin-rich corneocytes (bricks) are embedded within an intercellular lipid matrix (mortar).

Beneath the epidermis lies the dermis, also known as the corium, a firm connective tissue of mesodermal origin. It consists of a dense network of connective tissue with interwoven collagen fiber bundles and elastic tissue, particularly in the superficial layers [12]. The dermis also houses intricate networks of blood vessels, lymphatic channels, nerves, hair follicles, sweat glands, and sebaceous glands.

Transdermal Drug Delivery System

Transdermal drug delivery is a widely used and well-established method for administering medications. Compared to other delivery routes, it has gained significant attention due to its ease of use, patient compliance, and effectiveness [13]. This method is considered one of the safest, most convenient, and cost-efficient approaches to drug administration [14]. The primary objectives of

transdermal drug delivery systems (TDDS) include targeting specific sites of action and regulating the drug release rate to achieve optimal therapeutic effects [15]. These systems consist of self-contained dosage forms that, when applied to intact skin, facilitate controlled drug absorption into the systemic circulation [16].

A transdermal patch, commonly referred to as a skin patch, is a medicated adhesive applied to the skin that enables the controlled release of a drug into the bloodstream. TDDS patches are designed to maintain a steady drug delivery rate when placed on unbroken skin, ensuring consistent absorption. The goal of transdermal dosage formulation is to enhance drug permeability through the skin while minimizing retention and metabolic degradation [17]. This route of administration is recognized as an effective means for both localized and systemic drug delivery.

Transdermal drug delivery offers numerous advantages, including non-invasive and painless drug administration, sustained and controlled drug release, and the avoidance of degradation by stomach acids [18]. Additionally, it minimizes side effects compared to oral medications, provides an easier and more convenient alternative for individuals who struggle with oral drug intake, and serves as a cost-effective option for long-term therapy.

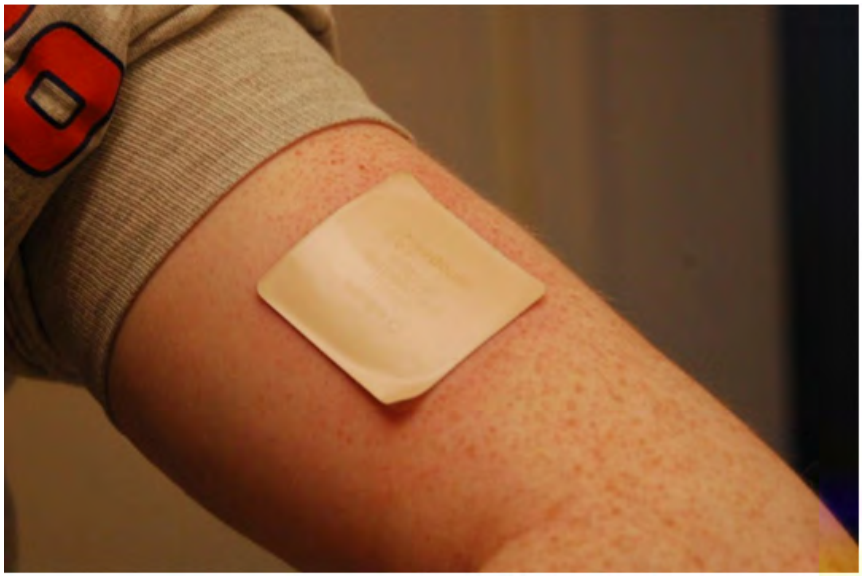


Figure 2: Transdermal Patch.

Advantages of Transdermal Drug Delivery [19]

- TDDS enables a steady release of medication through the skin, maintaining consistent drug levels in the bloodstream, which is essential for effective treatment.
- It serves as an alternative to oral drug administration, particularly for individuals who have difficulty swallowing pills.
- This system is beneficial for patients who are nauseated or unconscious, as it does not require active ingestion.
- It is especially useful for individuals with gastrointestinal issues, as the drug bypasses the stomach, preventing direct contact.
- Similar to intravenous infusion, TDDS provides a stable plasma drug concentration over time.
- In cases of toxicity or adverse reactions, the patch can be easily removed, halting further drug absorption.
- The convenience of TDDS lies in its simple application, making drug administration easier for patients.
- This delivery method bypasses the first-pass metabolism, enhancing drug bioavailability.
- It allows for prolonged drug action, reducing the frequency of dosing.
- Patients can self-administer the medication, promoting ease of use and adherence to therapy.

Disadvantages of Transdermal Drug Delivery System [20]

- Numerous hydrophilic drugs struggle to penetrate the skin or do so at a very slow rate, which can compromise their therapeutic effectiveness.
- The use of transdermal patches may lead to side effects such as itching, swelling (edema), and redness (erythema).
- The skin's barrier function varies among individuals, across different body sites, and with age.
- There is a potential risk of irritation at the drug application site.
- The transdermal drug delivery system (TDDS) can be cost-ineffective.

- This method is not suitable for acute conditions and is primarily used for chronic treatments.
- TDDS is incompatible with ionic drugs.
- There is a possibility of dose dumping.
- Drugs used in TDDS must exhibit an affinity for both lipophilic and hydrophilic environments.
- Achieving high systemic drug concentrations through this method is challenging.

Transdermal Patch

A transdermal patch is a medicated adhesive patch applied to the skin to administer a precise dose of a drug. This system allows the drug to penetrate the skin and enter the bloodstream at a controlled rate. Currently, the most widely available transdermal systems in the market utilize semi-permeable membranes and are commonly referred to as patches. Transdermal drug delivery systems (TDDS), also known as "transdermal patches" or "skin patches," are formulated to transport a therapeutically effective drug concentration through the skin and into systemic circulation [21].

Main Ingredients Used for the Preparation of Transdermal Patch

- **Backing Film**: This is the outermost layer of the transdermal patch, designed to shield the drug formulation while the patch is in use. It often serves as a surface for printing essential product details or usage instructions. In some cases, the backing also helps secure the drug formulation. Therefore, selecting a material with high durability and resilience is crucial [13].
- **Drug Formulation:** This refers to the active pharmaceutical ingredient(s) contained within the patch, which are gradually released and absorbed through the skin. It is sometimes known as the drug reservoir.
- **Membrane:** The membrane plays a key role in regulating the release rate of the drug formulation, ensuring controlled delivery to the skin.
- **Liner:** This protective layer covers the adhesive side of the patch and is removed just before application. Despite its simple function, the liner must be compatible with both the adhesive and the drug formulation while also being easy to peel off and compliant with regulatory standards.
- **Adhesive or Tape:** This is the layer that allows the patch to adhere securely to the skin using a biocompatible adhesive. It ensures the patch remains in place for effective drug delivery.

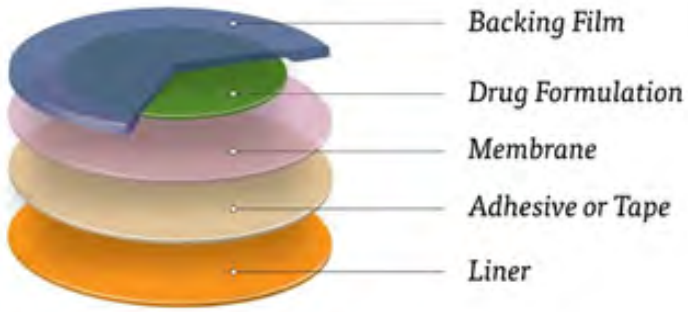


Figure 3: Basic Components of Transdermal Patch.

Classification of Transdermal Patch

The TDDS can be classified into two major categories [22]:

1. Rate Programmed Transdermal Patches
2. Physical Stimuli Activated Transdermal Patches

Rate Programmed Transdermal Patches

The developed patch-type TDDS can be described by three basic design
principles (the fourth being a specialised design):

1. Drug in reservoir (membrane type),
2. Drug in matrix (monolithic type).
3. Drug in adhesive (matrix), and
4. Drug in micro reservoir (reservoir in adhesive matrix).

Drug in Reservoir (Membrane Patch): In membrane patches, a delivery rate-controlling membrane is positioned between the drug reservoir and the skin. This membrane can be either microporous, where drug flux is regulated by pore size and tortuosity, or dense polymeric, allowing drug permeation through dissolution and diffusion. Various materials, such as ethylene-vinyl acetate copolymers, silicones, high-density polyethylene, polyester elastomers, and polyacrylonitrile, can serve as rate-controlling membranes. An ideal membrane should facilitate drug

and enhancer permeability (if used) while retaining other formulation excipients [13]. The drug reservoir may consist of diverse materials, from simple formulations like mineral oil to more complex ones, including aqueous-alcoholic solutions and gels, with or without co-solvents. A polymeric alcoholic reservoir system should support zero-order drug release throughout the delivery period, achieved by ensuring drug saturation in the reservoir material, often formulated as a suspension [17].

Drug in Matrix: In this drug delivery system, the active pharmaceutical ingredient is evenly distributed within a polymeric matrix, from which it diffuses to the skin surface [23]. This matrix, functioning as a drug reservoir, is typically composed of materials such as silicone elastomers, polyurethanes, polyvinyl alcohol, and polyvinyl pyrrolidone. The drug release process involves several key steps:

The drug molecules separate from their crystalline structure. They undergo solubilization or partitioning within the polymeric matrix.

The molecules then diffuse through the matrix until reaching the skin surface.

A controlled drug release following zero-order kinetics can be achieved if the drug remains at a saturated concentration within the matrix's fluid phase and its diffusion within the polymer is significantly faster than its permeation through the skin.

Drug-in-Adhesive Matrix: In these basic systems, the drug and enhancer are incorporated into an adhesive blend, which is then applied onto a backing layer, such as a polyester film, to create an adhesive patch. However, these systems present certain limitations:

Chemical interactions may occur, potentially affecting the adhesive's performance, leading to the degradation of active compounds, or generating new chemical entities.

The physicochemical properties of both the drug and adhesive matrix can influence drug release rates, particularly for hydrophilic and hydrophobic drugs [24]. For instance, the lipophilic nature of silicone adhesives restricts the solubility of hydrophilic drugs within the adhesive matrix.

Incorporating additional excipients, such as skin permeation enhancers, into the drug-in-adhesive system may alter both the drug release profile and the adhesive characteristics [20].

Drug in Microreservoir: This transdermal drug delivery system (TDDS) includes both reservoir and matrix-dispersion technologies. To construct the drug reservoir in this method, the drug is suspended in an aqueous solution of a water-soluble polymer [17]. This combination is then equally spread in a lipophilic polymer, resulting in the production of countless tiny drug reservoir spheres that are resistant to leaching. The dispersion, which is thermodynamically unstable, is stabilized by quick cross-linking of the polymer.

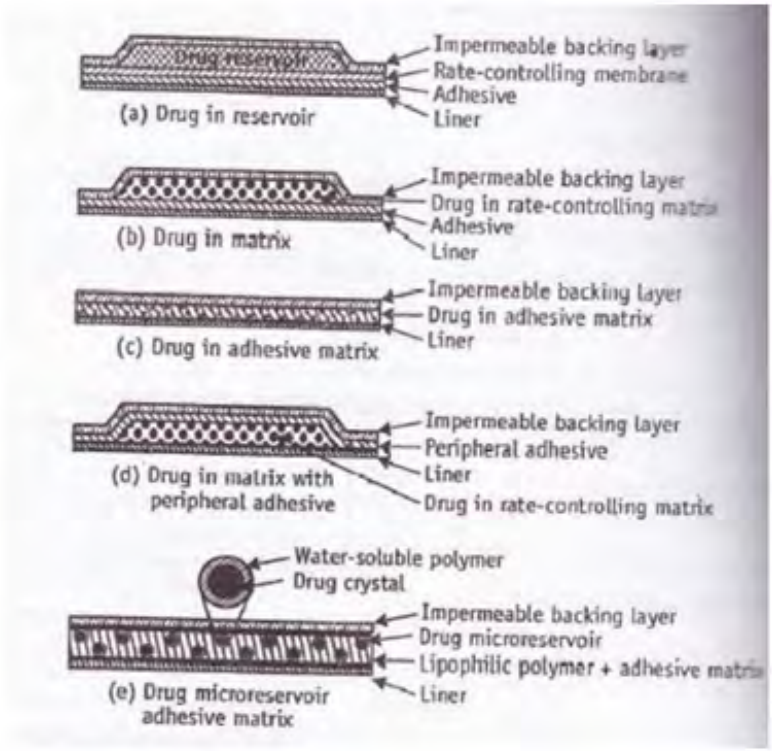


Figure 4: Different type of Rate Programmed Transdermal Patch.

Physical Stimuli-Activated Transdermal DDS

Transdermal delivery of drugs is not only possible through transdermal patches. but also through the use of methods involving physical stimuli, such as electrophoresis, electroporation, and sonophoresis. An example of structure-based system belonging to this class of TDDS is microneedles, developed by Alza and called Macroflux [16]. This system consists of a thin titanium screen with 200μm long microprojections attached to the underside (Figure 6.5). Such microneedles on application to the skin, create superficial pathways through the stratum corneum (which contains no nerves), without causing any pain to the receptors in the dermis as they are very short in length. Drugs can either be coated onto the micro-projections for bolus delivery or attached to a drug reservoir for continuous or iontophoretic application. This TDDS is suitable for delivering vaccines, small molecules, and biopharmaceuticals.

Physical stimuli-activated system types:

1. Structure-based systems, e.g., microneedles
2. Velocity-based systems, e.g., get propulsion
3. Electrically-based systems, e.g., microneedles
4. Iontophoresis
5. Electroporation
6. Sonophoresis
7. Photomechanical waves

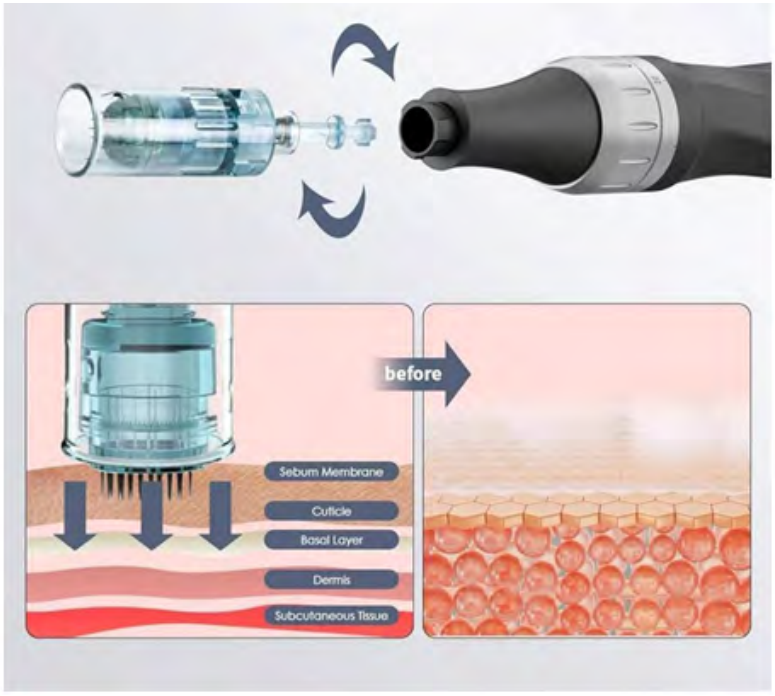


Figure 5: Microneddle System for Transdermal Drug Delivery System.

Mechanism of Action of Transdermal Patches

The application of the transdermal patch and the flow of the active drug constituent from the patch to the circulatory system via skin occur through various methods.

Following are the stages in drug delivery in a transdermal patch [25]:

1. Release of medicament from the vehicle.
2. Penetration through the skin barriers.
3. Activation of the pharmacological response.

The effectiveness of transdermal patches as a therapeutic method relies on the interplay of three key components: the drug, the vehicle, and the skin. These factors together influence the movement of drug molecules in systems such as transdermal drug delivery systems, which incorporate a rate-controlling membrane to manage percutaneous absorption. Initially, drug particles must dissolve in the vehicle, enabling molecules to diffuse toward the patch membrane. Once at the membrane, they cross it, diffuse through the polymer, and enter the skin adhesive. The drug molecules then move towards the interface between the vehicle and the stratum corneum, where they partition into the stratum corneum and continue to diffuse through it [26]. Some drugs may accumulate at a depot site, while others move deeper and encounter another interface, where they partition into the viable epidermis. For lipophilic substances, the partitioning coefficient may be less favourable (i.e., less than 1). Within the epidermis, enzymes may metabolize the drug or it may interact with receptors. Upon reaching the dermis, additional depot sites and metabolic activities can alter the drug's path before it enters the capillary system, where it

partitions into the capillary wall and enters the bloodstream for systemic circulation. A portion of the drug may also deposit into subcutaneous fat, creating another depot, and some may reach deeper muscle layers, which is observed in the effectiveness of non-steroidal anti-inflammatory drugs. However, several complicating factors exist, such as tissue non-homogeneity, the presence of lymphatics, interstitial fluid, hair follicles, sweat glands, cell division, and the transport of cells through the stratum corneum. Additionally, the disease state, healing process, drug formulation, and vehicle components can alter the skin barrier over time. As the vehicle ingredients penetrate the skin, they bring along cellular debris, sweat, sebum, and surface contaminants that change the physicochemical properties of the dermis. Emulsions may break down or invert when applied and volatile solvents may evaporate.

Arthritis

Arthritis is a medical disorder characterized by the swelling and discomfort in one or more joints. The most frequent symptoms are joint soreness and stiffness, which often increase with age. Osteoarthritis and rheumatoid arthritis are the two most frequent kinds of arthritis.

Osteoarthritis begins when the cartilage that cushions the ends of bones in a joint deteriorates. This breakdown causes to discomfort, oedema, and difficulties moving the joint. As the illness advances, the bones may begin to rub against each other, exacerbating discomfort and stiffness.

Rheumatoid arthritis, in contrast, is an autoimmune illness in which the immune system wrongly targets the joints, especially the lining of the joints. This causes inflammation, discomfort, and may ultimately result in joint damage and deformity [27].

There are many different varieties of arthritis induced by other reasons. For example, gout is a kind of arthritis characterized by the deposition of uric acid crystals in the joints owing to excessive amounts of uric acid in the circulation. Additionally, some infections or disorders like psoriasis or lupus might lead to distinct kinds of arthritis [28].

Treatment for arthritis relies on the individual form of arthritis and seeks to reduce symptoms and enhance the patient's quality of life. Treatment techniques frequently involve a combination of drugs, physical therapy, lifestyle modifications, and, in some circumstances, surgery. Medications are often used to treat pain and inflammation, while physical therapy helps increase joint mobility. Adopting a healthy lifestyle, including maintaining an optimal weight and participating in regular physical exercise, may also help reduce symptoms. In severe circumstances, surgical operations may be necessary to repair or replace damaged joints.

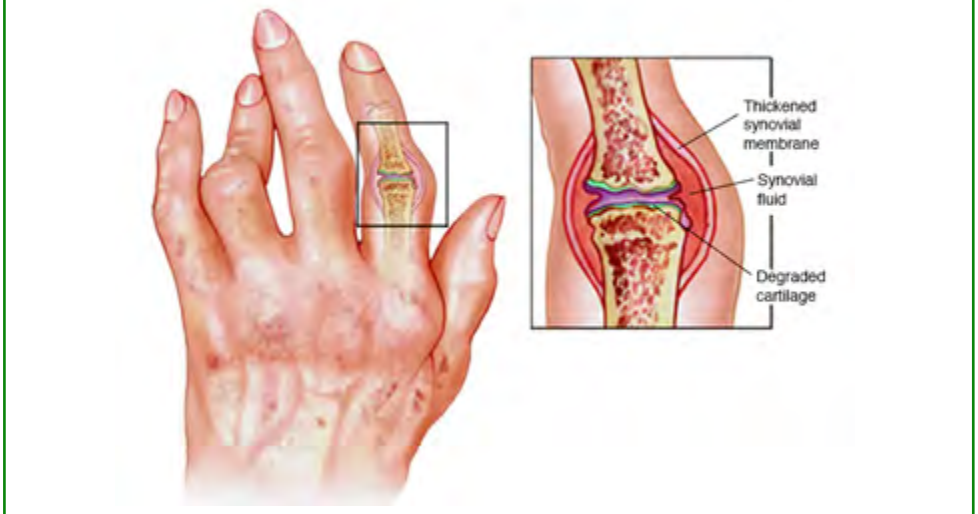


Figure 6: Rheumatoid Arthritis in Joints.

Risk factors

Risk Factors for Arthritis [29]

- **Family History:** Some forms of arthritis are hereditary, meaning if your parents or siblings have the condition, you may be more likely to develop it. Your genetic makeup can also make you more susceptible to environmental factors that might trigger arthritis.

- **Age:** The likelihood of developing various types of arthritis, including osteoarthritis, rheumatoid arthritis, and gout, increases as you get older.
- **Gender:** Women are more prone to developing rheumatoid arthritis compared to men, while gout, another type of arthritis, is more common in men.
- **Previous Joint Injury:** Previously injured a joint, especially through sports or physical activity, it can increase the risk of arthritis in that joint later in life.
- **Obesity:** Carrying excess weight places additional stress on weight-bearing joints, such as the knees, hips, and spine. This increases the risk of arthritis.
- **Complications:** Severe arthritis, especially in the hands or arms, can severely limit daily activities. In cases where weight-bearing joints are affected, it may become difficult to walk or sit up straight. Over time, joints might even become deformed or misaligned.

Rheumatoid Arthritis (RA): Rheumatoid arthritis is a chronic autoimmune disorder that primarily affects the joints, though it can also impact other organs such as the skin, eyes, lungs, heart, kidneys, and blood vessels. It disrupts joint function, significantly impairing the quality of life of those affected. RA is a common condition, affecting about 1% of the global population, or approximately 700 million people, with more than 80% of cases occurring in women [30].

RA treatment often involves non-steroidal anti-inflammatory drugs (NSAIDs), anti-rheumatic drugs, and glucocorticoids. Recent research has shown that natural plant extracts and compounds (NPECs) can be highly effective in reducing RA symptoms. Investigating these natural remedies further could offer new treatments for RA patients, improving their overall health and quality of life.

Pathogenesis of RA: RA susceptibility is largely influenced by genetic factors; estimates of heritability range from 50% to 60%. More than 30% of genetic risk is attributed to the human leukocyte antigen (HLA) locus, with other genes such as tumor necrosis factor-alpha (TNF-alpha) being implicated. The immune system and the synovium (joint lining) interact intricately to cause the illness. Inflammation is caused by important immune cells, including neutrophils, macrophages, mast cells, and dendritic cells. Phosphoinositide-3-kinase (PI3K) delta and gamma signaling molecules are implicated in the start of illness, and T cells and B cells generate cytokines, antibodies, and immunological complexes. An imbalance in T-helper (TH) cell subtypes, including TH1, TH17, and regulatory T (Treg) cells, which are essential for the development and course of RA, is the cause of inflammation [31].

S. No.	Common name	Botanical name	Chem. constituents	Uses
1	Ginger	Zingiber officinale	Gingirol, shogaol, zingibrene, Zingiron, curcumin	Anti-inflammatory, pain relieving effect
2	Turmeric	Curcuma longa	Turmeron, alpha-turmerone, beta-turmirone	Ant-inflammatory, reduce pain, increase blood circulation
3	Camphor oil	Cinnamomum camphora	Camphor, cineol, eugenol, limonene, safrol	Analgesic, anti-inflammatory, antiseptic, anti-infective
4	Peppermint	Mentha piperita	menthol	Relieves muscle and bone pain
5	Clove oil	Syzgiumar omaticum	Eugenol, acetyleugenol, vanillin, tannins	Anti-inflammatory
6	Eucalyptus oil	Eucalyptus	1,8-cineole, pinene, myrcene	Anti-inflammatory
8	Aloe vera	Aloe barbadensis	Vitamins, enzymes, minerals, hormones	Anti-inflammatory
9	Neem	Azadirachta indica	Betasitosterol, azadiractin, myricetin, nimbiol, quercetin	Pain releving, anti-inflammatory
10	Herbasieg esbeckiae	Sigesbeckia orietalis L	Sesquiterpenoids, diterpenoids, flavonoids	Anti-inflammatory, antitumor, antiallergis, antithrombotic
11	Wintergreen oil	Globulus	Terpinene	Analgesic, improve circulation
12	Indian borage	Trichodesma indicum	Hexacosane, oleic, linoleic, palmitic and srearic acid	Thermogenic, emollient, anti-inflammatory
13	Salai guggul	Boswellia serrata	Boswellic acid, acetyle-beta-boswellic acid	Anti-inflammatory
14	Katuvari	Capsicum annum	Capsoicin	Reduce swelling, rheumatoid arthritis, osteoarthritis

Table 1: Herbal Drugs Used in Rheumatoid Arthritis [28].

Selection of Herbs

Drug	Ginger	Turmeric
Scientific Name	*Zingiber officinale*	*Curcuma longa*
Family	Zingiberaceae	Zingiberaceae

Table 2: Drug and their Scientific Name & Family.

Ginger

The main benefit of ginger (*Zingiber officinale Roscoe*, Zingiberaceae), a popular plant in the US, is that it has anti-emetic qualities. But since ancient times, it has also been utilized medicinally as an anti-inflammatory. In contemporary use, special emphasis has been placed on the phenolic compounds called gingerols, which give ginger its strong flavor, and their potential to treat inflammatory conditions like arthritis by inhibiting the enzyme cyclooxygenase (COX). In an animal model of rheumatoid arthritis (RA), we previously showed that ginger extracts containing gingerol have strong anti-arthritic properties [26].

Anti-inflammatory Effects

- **Gingerols and Shogaols:** These are the primary active compounds in ginger responsible for its anti-inflammatory effects. They inhibit the production of pro-inflammatory cytokines and enzymes, such as COX-2, similar to the action of non-steroidal anti-inflammatory drugs (NSAIDs).
- **Reduction of Pro-inflammatory Mediators:** Ginger reduces the levels of TNF-α, IL-1β, and IL-6, which are key mediators in the inflammatory process associated with RA.

Antioxidant Properties

- **Neutralization of Free Radicals:** Ginger contains antioxidant compounds that help neutralize free radicals, reducing oxidative stress and damage in joint tissues.
- **Enhancement of Antioxidant Enzymes:** It boosts the activity of endogenous antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase.

Immunomodulatory Effects

- **Modulation of Immune Response:** Ginger affects the activity of various immune cells, including macrophages and T cells, which play a role in the autoimmune response seen in RA.

Figure 7: Ginger Rhizomes.

Turmeric

Curcumin is a natural polyphenol and the major ingredient from the rhizome of Turmeric (*Curcuma longa*) and other Curcuma species. It has been extensively utilized for many medicinal objectives, such as treatment of pain and inflammatory conditions in various illnesses [32].

Curcumin, the principal curcuminoid, is recognized for its broad spectrum of biological activities, including regulating inflammation, cell growth, and apoptosis. These properties make turmeric useful for both preventing and treating

various health conditions due to its potent antioxidant and anti-inflammatory effects, and it is generally considered safe for consumption. Curcumin's ability to interact with numerous molecular targets underpins its pleiotropic nature, contributing to its potential as a therapeutic agent.

Anti-inflammatory Effects: Curcumin inhibits several molecules involved in inflammation, such as:

- **Nuclear factor-kappa B (NF-κB):** A protein complex that controls the transcription of DNA, cytokine production, and cell survival.
- **Cytokines:** Proteins such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) that play crucial roles in promoting inflammation.
- **Enzymes:** Curcumin inhibits enzymes like cyclooxygenase-2 (COX-2) and lipoxygenase (LOX), which are involved in the inflammatory process.

Antioxidant Properties: Curcumin neutralizes free radicals and increases the activity of antioxidant enzymes, reducing oxidative stress which is often elevated in RA patients.

Immunomodulatory Effects: Curcumin modulates the immune response, reducing the activity of immune cells that attack the joints in RA.

Curcumin has garnered particular interest as a potential treatment for rheumatoid arthritis (RA) due to its antioxidant capabilities and its influence on inflammation-related agents. Currently, curcumin is available in various forms such as beverages, pills, capsules, lotions, gels, nasal sprays, and extracts, and is used as both a food additive and for medicinal purposes.

Figure 8: Turmeric.

Extraction of the Drugs

Solvent Extraction Method

The solvent extraction method has been used widely for the extraction and separation of elements and biocompounds. Water, methanol, ethanol and hexane are the most commonly used solvents in this technique [33].

Extraction of Ginger

Material Used: Dried Ginger Powder, Acetone

Method:

1. Prepare the ginger sample: Clean fresh ginger is sliced and dried in an oven at 55-60°C. The dried ginger is then ground into a powder of 60-80 mesh size.
2. Load the sample: The ginger powder is loaded into a thimble and placed in the main chamber of the Soxhlet extractor.
3. Select the solvent: Acetone is used as a solvent for extraction. (Operational Conditions - Heating temperature: 80°C, Heating time: 1 2 4 6 8hrs, Ratio: 30gm of ginger and 100ml of solvent)
4. Extraction: The solvent is heated and vaporizes, condenses in the condenser, and drips into the thimble containing the ginger powder. The solvent extracts the ginger oil and fills the siphon tube, emptying the extracted oil into the distillation flask. This cycle repeats for 4-8 hours.
5. Separation: After extraction, the solvent is separated from the ginger oil by evaporation. The ginger oil remains as the final product.

Result: Ginger Oil Extracted: 28mL.

Figure 9: Weighing of ginger for thimble preparation.

Figure 10: Extraction of Ginger.

Extraction of Turmeric

Material Used: Dry Turmeric, Methanol

Method:

1. Prepare the turmeric sample by cleaning, washing, slicing, and drying the fresh rhizomes in the sun for one week, followed by oven drying at 50°C for 6 hours. Grind the dried rhizomes into a powder using an electronic mill.
2. Weigh out 6 grams of the turmeric powder and place it into a thimble. Insert the thimble into the main chamber of the Soxhlet extractor.
3. Add 250 mL of the desired solvent (e.g., chloroform, methanol, or acetone) to a round-bottom flask and attach it to the bottom of the Soxhlet extractor.
4. Heat the solvent in the flask, causing it to vaporize and condense in the condenser. The condensed solvent drips into the main chamber containing the turmeric powder, extracting the curcuminoids.
5. When the solvent level reaches the siphon tube, the extracted solution is siphoned back into the round-bottom flask, completing one extraction cycle. Repeat this cycle for 7 hours.
6. After extraction, concentrate the dark brown extract using a rotary evaporator to obtain the crude curcuminoid extract.

Result: Turmeric extract collected: 40mL.

Figure 11: Extraction of Turmeric.

Thin Layer Chromatography

A thin-layer chromatography (TLC) method has been developed and validated for the quantitative analysis of gingerols, the major bioactive compounds in ginger (Zingiber officinale) and curcuma longa (main chemical constituent of Turmeric).

Figure 12: Turmeric and Ginger Extract.

For Zingiber officinale

When analyzing Zingiber officinale (ginger) using TLC, the following detailed process can be followed:

Materials Required

1. Sample Preparation
- Zingiber officinale extract
- Solvents for extraction (e.g., methanol or ethanol)

2. TLC Plate
- Pre-coated silica gel G plate

3. Mobile Phase
- Toluene
- Ethyl acetate
- Formic acid

4. Developing Chamber
- TLC developing tank with a lid

5. Application Tools
- Capillary tubes or micropipette

6. Detection Methods
- UV light source
- Chemical reagents for staining (e.g., iodine vapors, vanillin-sulfuric acid spray)

Procedure

1. Sample Preparation
- Extract the active compounds from Zingiber officinale by using an appropriate solvent such as methanol or ethanol. Filter the extract to remove any solid particles.

2. Preparation of the TLC Plate
- Use a pre-coated silica gel G plate. Handle the plate by its edges to avoid contamination.
- Mark a baseline about 1-2 cm from the bottom of the plate using a pencil. Do not use a pen as the ink might interfere with the results.

3. Spotting the Sample
- Using a capillary tube or a micropipette, apply small spots of the Zingiber officinale extract onto the baseline of the TLC plate. Spot multiple times at the same point to ensure enough sample is applied, allowing each application to dry before the next.

4. Preparation of the Mobile Phase
- Mix the solvents in the specified ratio of 9:1:2 (Toluene: Ethyl acetate: Formic acid). Ensure thorough mixing to create a homogeneous mobile phase.
- Pour the prepared mobile phase into the developing chamber to a depth of about 0.5 cm. Cover the chamber with a lid and allow it to saturate with the solvent vapors for about 10-15 minutes.

5. Development of the TLC Plate
- Carefully place the spotted TLC plate into the developing chamber, ensuring the spots are above the solvent level.
- Cover the chamber and allow the mobile phase to ascend the plate by capillary action.
- When the solvent front is about 1-2 cm from the top of the plate, remove the plate and mark the solvent front immediately with a pencil. Allow the plate to dry in a fume hood.

6. Visualization of Spots
- Applying a chemical reagent like iodine vapours in iodine chamber to the plate to visualize non-fluorescent compounds.

7. Analysis
- Measure the distance travelled by each spot and the distance travelled by the solvent front. Calculate the Rf values using the formula:
- **Rf Value of Zingiber officinale**

Distance Travelled by Solute / Distance Travelled by Solvent = 5.5 / 6.3 = 0.873.

For Curcuma longa L

When analyzing Curcuma longa L (turmeric) using TLC, the following detailed process can be followed

Materials Required:
- Curcuma longa extract: The sample to be analyzed.
- Silica gel G: The stationary phase.
- Mobile phase solvents: Chloroform, methanol, and formic acid.
- TLC plates: Pre-coated with silica gel G.
- Capillary tubes: For spotting the sample onto the TLC plate.
- Developing chamber: A container to develop the TLC plate.
- UV lamp or iodine chamber: For visualizing the spots.

Procedure

1. Preparation of TLC Plate:
- Cut the TLC plate to the desired size (usually 5 cm x 10 cm).
- Using a pencil, lightly draw a straight line across the plate about 1 cm from the bottom. This is the origin line where the sample will be applied.
- Make small marks along the origin line to indicate where

each sample will be spotted.

2. Preparation of Mobile Phase:

- In a clean container, mix the mobile phase solvents in the specified ratio: 48 parts chloroform, 2 parts methanol, and 0.5 parts formic acid [34].
- Pour this mixture into the developing chamber to a depth of about 0.5 cm. Close the chamber and allow it to saturate with the solvent vapor for about 15-30 minutes.

3. Spotting the Sample:

- Using a capillary tube, take a small amount of the Curcuma longa extract.
- Spot the extract onto the marked points on the origin line of the TLC plate. Ensure the spots are small and concentrated.
- Allow the spots to dry before placing the plate in the developing chamber.

4. Developing the TLC Plate:

- Carefully place the TLC plate into the developing chamber, ensuring that the solvent level is below the origin line.
- Close the chamber and let the solvent ascend the plate by capillary action.
- Allow the solvent front to rise to about 1 cm from the top of the plate.

5. Removing and Drying the Plate:

- Once the solvent front has reached the desired height, remove the TLC plate from the chamber.
- Mark the solvent front with a pencil immediately.
- Allow the plate to dry completely.

6. Visualization of Spots:

- Examine the dried plate under a UV lamp. Many compounds, including those in Curcuma longa, fluoresce under UV light.
- Alternatively, place the plate in an iodine chamber to visualize the spots.
- Mark the positions of the visible spots with a pencil.

7. Analysis:

- Measure the distance travelled by each spot from the origin line.
- Measure the distance travelled by the solvent front from the origin line.
- Calculate the Rf value for each compound using the formula:
- **Rf Value of Curcuma longa L**

Distance Travelled by Solute / Distance Travelled by Solvent = 6.1 / 7.3 = 0.83.

Figure 13: Visualizing of spots in iodine chamber.

Figure 14: TLC of Turmeric and Ginger.

Material Required

- Turmeric (Curcuma longa L)
- Ginger rhizomes (Zingiber officinale)
- Distilled Water
- Hydroxy Propyl Methyl Cellulose (HPMC)
- Propylene Glycol
- Polyethylene Glycol (PEG 400)
- Glycerin
- Elastic Adhesive Tape

SNO.	INGREDIENTS	QUANTITY
1	Turmeric (*Curcuma longa L)*	0.5 mL
2	Ginger rhizomes (*Zingiber officinale*)	0.5 mL
3	Distilled Water	80 mL
4	HPMC 15	6gm
5	Propylene Glycol	0.5mL
6	PEG 400	5 mL
7	Glycerine	0.1 mL

Table 3: Ingredients Used for Formation of Patch.

Equipments Used: Magnetic Stirrer, Beaker, Petridish, Ointment Base, Ointment Spatula, Weighing Balance

Method of Preparation

Preparation of HPMC Solution:

- Weigh 6 grams of HPMC 15 and transfer it into a beaker.
- Measure 80 ml of distilled water and add it to the beaker containing HPMC 15.
- Allow the mixture to sit overnight to ensure the HPMC is fully hydrated and dissolved in the water.

Dissemination with Magnetic Stirrer:

- After overnight hydration, place the beaker on a magnetic stirrer.
- Stir the solution continuously to ensure uniform dispersion of HPMC in the water, creating a homogeneous solution.

Addition of PEG 400:

- Measure 5 ml of PEG 400.
- Slowly add the PEG 400 to the HPMC solution while stirring. This acts as a plasticizer, which will improve the flexibility and durability of the resulting patch.

Incorporation of Extracted Drug:

Measure 0.5 ml of the extracted drug. (Zingiber officinale & Curcuma longa L)

- Add the drug extract to the HPMC-PEG 400 mixture while continuing to stir. Ensure the drug is evenly distributed throughout the solution.

Incremental Addition of Propylene Glycol and Glycerin:

- Gradually add propylene glycol and glycerin to the mixture. These components act as additional plasticizers and humectants, helping to maintain the patch's moisture balance and flexibility.
- Continue adding these components incrementally and stirring until the mixture reaches complete dissolution, forming a clear and homogeneous solution.

Formation of Patches:

- Prepare glass petri dishes by cleaning them thoroughly.
- Pour the resulting homogeneous solution into the glass petri dishes, spreading it evenly to form a thin film.
- Allow the solution in the petri dishes to dry at room temperature or in a controlled environment to form the transdermal patches.

Drying and Storage:

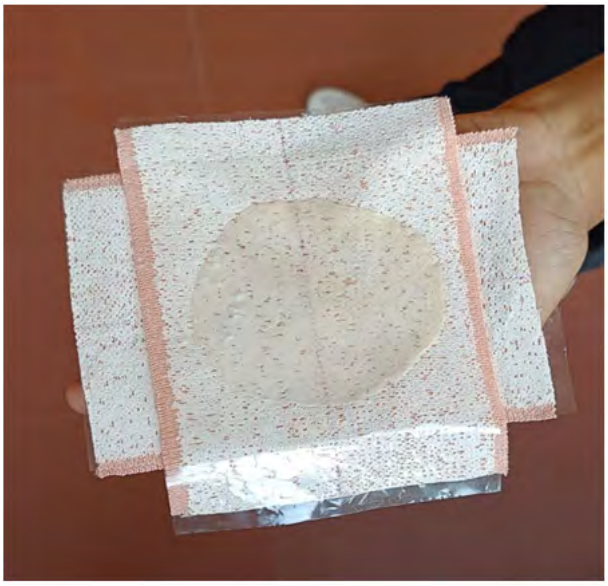
- Once the patches are dried, carefully remove them from the petri dishes.
- Store the patches in an airtight container to protect them from moisture and contamination until further use.

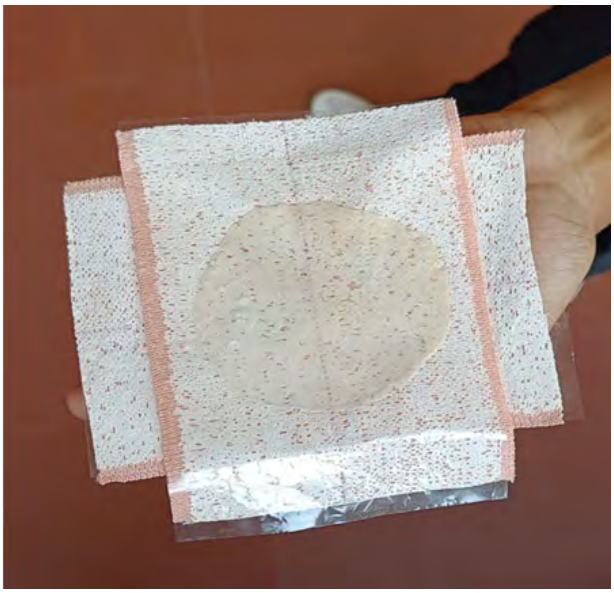
During The Preparation of Transdermal Patch

Figure 15: Stirring the solution for Homogeneous Solution.

Figure 16: Formulation of Transdermal Patches Using Solvent Casting Method.

Figure 17: Peeling off the Patch.





Figures 18 & 19: Pictures of the Prepared Patches.

Figure 20: Packing f Herbal Patches.

Evaluation of Transdermal Patches

1. Skin Irritation Evaluation [35]

- Apply a small portion of the transdermal patch to the skin (typically the upper arm or back) of human volunteers.
- Secure the patch with adhesive tape and leave it in place for some hours.
- Assess the skin for signs of erythema (redness), edema (swelling), itching, or other irritation reactions.
- Grade the skin reactions according to a standardized scoring system, such as the draize scoring system.
- Repeat the test with a control patch (e.g., placebo patch) for comparison

Result

The transdermal patch was well-tolerated, with no evidence of erythema, edema, or itching observed in any of the volunteers after some hours of patch application. The scores for skin irritation were all zero, indicating no irritation potential.

2. Organoleptic Characteristics

- The physical appearance of developed patch was evaluated by using a naked-eye examination for its appearance, colour, clarity, flexibility, and smoothness.

Result

The transdermal patch is of yellow colour. It is smooth in texture and has enough flexibility.

3. Thickness Of Patch

A Vernier caliper was used to measure patch thickness uniformity at six different places. The mean thickness of all six places was then determined.

4. Uniformity Of Weight

Each of the three patches were weighted for each batch, and the mean weight were determined.

5. Folding Endurance

Folding endurance was evaluated by folding the patches repeatedly in the same area even after it broke. Folding endurance is the number of times the patches can be folded in the same area without breaking.

6. Determination Of Surface Ph

The pH of the patch is evaluated by swelling it with 1 ml of distilled water for two hours at room temperature before use. Then, place the pH electrode on the patch's surface to record the pH value and make them to adjust itself for 1 minute [36,39].

7. Percent Moisture Content

The percent moisture content of the patches was determined by weighing the patches after placing them inside a desiccator for 24 hours. The percent moisture content can be calculated using the following formula:

$$\textit{Percentage Moisture content} = \textit{Initial weight} - \textit{Final weight} \,/\, \textit{Initial weight} \times 100$$

Formulation Code	Thickness (mm)	Weight Uniformity (gm)	Folding Endurance (n)	Surface pH	% moisture content
F1	0.434 ± 0.02	0.1850 ± 0.002	15 ± 2.60	6	3.96 ± 0.86
F2	0.434 ± 0.01	0.1866 ± 0.002	12 ± 3.21	6	2.67 ± 0.50
F3	0.434 ± 0.01	0.1876 ± 0.003	13 ± 2.50	6	2.48 ± 0.31

Table 4: Evaluation of Herbal Transdermal Patch.

Conclusion

All three formulations (F1, F2, and F3) have a consistent thickness of approximately 0.434 mm with minimal variation, indicating good control over the manufacturing process. The weight uniformity across the formulations is fairly consistent, with F1 (0.1850 gm), F2 (0.1866 gm), and F3 (0.1876 gm). The low standard deviations suggest uniform distribution of the patch components. F1 exhibits the highest folding endurance (15 ± 2.60), indicating superior flexibility and mechanical strength compared to F2 (12 ± 3.21) and F3 (13 ± 2.50). This suggests that F1 may be more durable during application and use. All formulations have a surface pH of 6, which is close to the skin's natural pH, suggesting that these patches are likely to be non-irritating and suitable for transdermal application. F1 has the highest moisture content (3.96 ± 0.86), followed by F2 (2.67 ± 0.50) and F3 (2.48 ± 0.31). The moisture content is crucial for maintaining the flexibility and adhesion of the patch. F1's higher moisture content might contribute to its better folding endurance.

Among the three formulations, F1 stands out due to its higher folding endurance and moisture content, which may contribute to better mechanical properties and comfort during use. However, all formulations exhibit acceptable thickness, weight uniformity, and surface pH, making them potentially suitable for transdermal applications. Further optimization and testing may be necessary to balance the moisture content and folding endurance to enhance the overall performance of the patches.

The development of a herbal transdermal patch utilizing Turmeric and Ginger extracts represents a promising alternative for the management of joint pain. This innovative approach leverages the well-documented anti-inflammatory and analgesic properties of these herbal extracts to provide effective pain relief.

The extraction process involves isolating the active bioactive compounds from Turmeric and Ginger, ensuring a high concentration of therapeutic agents. This process is critical to preserving the efficacy of the extracts, which form the cornerstone of the transdermal patch's therapeutic action. The formulation strategy is meticulously designed to optimize the patch's physicochemical properties, such as adhesion, flexibility, and controlled drug release. By incorporating appropriate solvents and excipients, the formulation ensures the stability and bioavailability of the active ingredients, thereby enhancing the overall therapeutic efficacy.

The study's outlined extraction process and formulation strategy provide a robust foundation for further research and clinical evaluation. Future studies can focus on optimizing the extraction methods to yield higher concentrations of bioactive compounds, as well as refining the formulation to improve patch adhesion and wearability. Clinical trials will be essential to evaluate the efficacy and safety of the transdermal patch in a broader patient population, providing valuable data to support its potential use in clinical practice.

Result and Discussion

The extraction process yielded concentrated herbal extracts rich in bioactive compounds, which serve as the active pharmaceutical ingredient (API) for the transdermal patch. The formulated patch exhibited desirable physicochemical properties, including flexibility, durability, and controlled drug release characteristics. In vitro studies demonstrated the patch's ability to permeate through the skin barrier and deliver therapeutic levels of the active ingredients.

The utilization of Turmeric and Ginger extracts in the development of a transdermal patch offers several advantages over conventional oral medications. Transdermal delivery bypasses the first-pass metabolism, leading to improved bioavailability and reduced systemic side effects. The controlled release of active ingredients ensures sustained pain relief, enhancing patient compliance and convenience. The choice of extraction solvent and formulation excipients influenced the potency and composition of the API, contributing to the efficacy of the transdermal patch.

The concentrated herbal extracts obtained from the extraction process were found to be rich in bioactive compounds, effectively serving as the active pharmaceutical ingredient (API) for the transdermal patch. These extracts, derived from Turmeric and Ginger, were meticulously formulated to ensure that the resulting patch exhibited optimal physicochemical properties such as flexibility, durability, and a controlled drug release profile.

Comprehensive in vitro studies have validated the patch's ability to effectively permeate the skin barrier, successfully delivering therapeutic levels of the active ingredients. This ability to facilitate transdermal delivery presents several significant advantages when compared to traditional oral medications. Notably, transdermal delivery bypasses the hepatic first-pass metabolism, thereby enhancing the bioavailability of the active compounds and reducing the risk of systemic side effects.

Moreover, the controlled release mechanism embedded within the patch ensures a sustained release of the active ingredients, providing prolonged pain relief. This feature is particularly beneficial for patient compliance, as it reduces the frequency of administration and enhances overall convenience.

The selection of appropriate extraction solvents and formulation excipients played a crucial role in determining the potency and composition of the API. This careful selection process contributed to the overall efficacy of the transdermal patch, underscoring the importance of formulation science in the development of effective transdermal therapeutic systems.

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