EFFECTS OF CASTOR OIL ON BIOADHESION AND DICLOFENAC POTASSIUM RELEASE FROM TRANSDERMAL FILMS

BY

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FEBRUARY, 2025.

CERTIFICATION

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DEDICATION

This work is dedicated to God Almighty, the one who made me firm, and strong throughout my journey in pharmacy school.

ACKNOWLEDGMENTS

My unreserved and profound gratitude goes to God Almighty, the greatest and most important personality in my journey. Also, my lovely mother for the hard sacrifices and her encouragement that saw me through to the completion of this work and throughout my journey in Pharmacy School, University of Benin.

I am grateful to my supervisor, Prof. Matthew I. Arhewoh, for his constructive corrections, sacrifices, enriched ideas, support and unwavering interest in this work, which was a great source of motivation.

My heart is full of love for my wonderful family for their loving care and support throughout my journey in Pharmacy school. My loving mother and my amazing siblings, Timothy Akande, Ernest Akande, and Benedicta Akande, your belief in me and endless display of love and support have been my greatest source of strength. My heart is filled with profound appreciation for each of you.

I am deeply grateful to my incredible friends, Ayobami Tiamiyu, Chinedu Abuwa, Denis Oriere, Chioma Ike, Idara Akpan, Moses Joy, Janet Akande, Solomon Oluwafemi, Emmanuel Samuel, Benjamin Samuel, El-Elohim Emmanuel, Zino Oboroh, Oreva Oboroh, Favour Dania, Victory Ogunmola, Esther Akpan, Hillary Segun. Your unwavering support and companionship have been a beacon of light on this journey. Words cannot express the depth of my gratitude for your genuine friendship. I cherish each of you immensely!

My heartfelt appreciation goes to some special and dear people in my life, Faith George, Mojisola Onaivi, Jacob Emmanuel, Kunle Ekun, Anita Duke, Eric Okomado, Idehen Osagiede,

Jude Joseph and Onimisi Emmanuel for their invaluable contributions and sacrifices that have played a pivotal role in the success of my education.

I am deeply thankful to The CHURCH OF CHRIST, UNIBEN/UBTH for being my ‘home away from home’, shout out to the flourishing leadership structure of the Church and to my mentors, Eric Okomado, Idehen Osagiede, Philemon Okpokpa, Titus Jude, Akpobome Akpughe, and Ogaga Akpughe for making it extra special. You have truly made my university journey unforgettable, and I'm so grateful for all the support.

Finally, my warm appreciation goes to all my colleagues and classmates especially to my project partners for their support and co-operation as we navigated our way from start to finish of the project work.

ABSTRACT

Background: Transdermal drug delivery (TDD) systems offer a non-invasive and efficient means of administering therapeutic agents in a controlled manner.

Purpose: To investigate how the incorporation of castor oil affects diclofenac potassium transdermal films.

Methods: Patches of diclofenac potassium were prepared using the solvent casting method. Patches labelled PQ0, PQ1, PQ2, PQ3, PO1, PO2, PO3 were prepared by dissolving a combination of measured amount of HPMC and diclofenac potassium in distilled water. Next, calculated amount of Tween 80 and castor oil were added. This mixture was then agitated for approximately five minutes to form a slur, then poured into a petri dish and allowed to air dry for 48 hours. Air-dried patches were cut into ten 1x1cm^2 sections. Cut patches were evaluated for their physicochemical properties, bioadhesion, drug content, folding endurance, *in vitro* and *ex vivo* release profile.

Results: Physicochemical tests demonstrated slightly varying weight and thickness, but were still within the pharmaceutically acceptable range of 5 ± 10% according to the USP. Bioadhesion test showed an increase with reduction in percentage of castor oil (5%). Highest bioadhesion obtained from a batch with oil was 2.90g/sec (batch without oil gave bioadhesion of 3.60 g/sec). Evaluation for the drug content demonstrated no significant difference. Also, folding endurance test demonstrated a good range between 200 - 400 folds. *In vitro* and *ex vivo* tests showed a better release with batches where the drug was dispersed in the oily phase with *ex vivo* peaking 80% release.

Conclusion: This study suggests that transdermal patches formulated by dispersing drug in the lowest percentage of oil possible (in this case, 5%) promises good bioadhesion and better diclofenac release across skin.

Keywords: Bioadhesion, castor oil, diclofenac films, drug diffusion, transdermal patch.

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CHAPTER ONE

1.1 Introduction

1.1.1 An overview of inflammatory pain

The term 'inflammatory pain' describes the heightened emotional and perceptual sensitivity to unpleasant stimuli that results from an inflammatory response linked to tissue damage (Wallace *et al.,* 2006). Acute inflammation is normally the body's protective reaction to infection or tissue injury, and it may cause pain while the damaged tissues are being removed and rebuilt (Peretz *et al*., 2004). Because inflammation resolution results in less nerve stimulation, inflammation control generally effectively reduces inflammatory pain. However, because inflammatory mediators act on pain-sensitive nerve terminals by lowering neuronal excitability thresholds and raising firing rate sensitivity, creating peripheral and central sensitization, chronic inflammation can result in unpleasant pain (Peretz *et al*., 2004). Usually, a combination of neuropathic and inflammatory factors contributes to persistent pain. Neuronal injury brought on by inflammatory mediators can set off an inflammatory response. Reduced physical activity, poor psychological states such as worry and depression, a poor quality of life, and significant financial load are all consequences of these unpleasant and complicated pain problems. We can improve the effectiveness of pain management and lessen societal burdens by comprehending the processes and treatments of inflammatory pain. (Biddle *et al.,* 2021).

1.2. Causes of inflammatory pain

Numerous conditions can result in inflammatory discomfort, such as

i. Diseases: Localized or systemic inflammation can be brought on by bacterial, viral, or fungal diseases.

ii. Autoimmune disorders: Chronic inflammation brought on by diseases like lupus and rheumatoid arthritis results in persistent discomfort.

iii. Tissue injury: As part of the healing process, inflammation is brought on by trauma, surgery, or burns.

iv. Neuropathic conditions: Inflammation is frequently a contributing factor to pain in diseases that impact the nerve system.

v. Chronic inflammatory diseases: Inflammatory pain is a sign of conditions like asthma and Inflammatory Bowel Disease (IBD) (Craft *et al.,* 2022).

1.3. Pathophysiology of inflammatory pain

A series of events contribute to inflammatory pain; it begins with tissue damage.

i. Initial injuries and mediators' release; resident tissue cells and immune cells (mast cells, macrophages) are activated by tissue injury. Prostaglandins (from cyclooxygenase activity), bradykinin, substance P, and cytokines are released as inflammatory mediators (Robi *et al.,* 2013).

ii. Sensitization of the periphery primary nociceptors are triggered and made more sensitive by inflammatory mediators. To lower the activation threshold, ion channels such as sodium channels and Transient Receptor Potential Vanilloid 1 (TRPV1), which is heat-responsive are regulated.

iii. The sensitization of the center; The spinal cord's dorsal horn neurons alter as a result of continuous nociceptive input. Prolonged potentiation and pain amplification are caused by increased activation of N-Methyl-D-aspartate (NMDA) receptors and neuropeptides such as substance P and Calcitonin Gene-Related Peptide (CGRP) (Austin *et al.,* 2013).

1.4. Symptoms of inflammatory pain

The symptoms of inflammatory pain include:

i. Redness: A result of the area receiving more blood
ii. Heat: Also brought on by elevated metabolic activity and blood flow.
iii. Swelling: Caused by the tissues accumulating fluid.
iv. Pain: Caused by pressure on neurons and the release of substances such as prostaglandins.
v. Loss of function: Pain or swelling may cause the affected part to not function as it should (Schrepf *et al.,* 2014).
vi. Hyperalgesia: an elevated reaction to painful stimuli
vii. Allodyna*:* pain in reaction to typically painless stimuli (Suer *et al.,* 2021).

1.5. Diagnosis of inflammatory pain

Identification diagnoses include:

i. Clinical Examination: Determining the features of pain and indications of inflammation.
ii. Laboratory Tests: Increased levels of pro-inflammatory cytokines, Erythrocyte Sedimentation Rate (ESR), and CRP (C-Reactive Protein). These are the laboratory markers for inflammation (Alivernini *et al.,* 2020).

iii. Imaging Studies: To detect inflammation in the joints or tissues, use Magnetic Resonance Imaging (MRI), ultrasound, or X-rays (Breidthardt *et al.,* 2018).

1.6. Management of inflammatory pain

Reducing inflammation and managing discomfort are the main goals of treatment. This comprises:

1.6.1. Interventions with pharmacology

i. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): Lower the production of prostaglandins (e.g., diclofenac, ibuprofen). A wide variety of inflammatory mediators are inhibited by corticosteroids. This is why they are referred to as high-ceilings inhibitors of pain (Noe, 2020).

ii. Disease-Modifying Anti-Rheumatic Drugs (DMARDs) are used to treat autoimmune diseases.

iii. Biologics: Tissue Necrosis Factor (TNF) inhibitors like infliximab target particular cytokines (Thorp, 2008).

1.6.2. Interventions without drugs

i. Physical therapy to keep one's function intact. To lessen localized discomfort and swelling, use hot or cold therapy.

ii. Cognitive-behavioral therapy for the treatment of chronic pain (Rayegani, 2012).

The goal of ongoing inflammatory pain research is to advance knowledge and care. This covers the optimization of newer routes of NSAIDs administration like the transdermal patch delivery system, cutting-edge drugs, etc. (Sharma *et al.,* 2014).

1.7. Overview of diclofenac potassium

Diclofenac potassium is a common NSAIDs. It is a fast-acting, water-soluble salt version of the medication. It is mostly used to treat fever, inflammation, and pain brought on by a number of illnesses, such as migraines, musculoskeletal diseases, physical trauma, and postoperative pain (Azzopardi, 2007). For circumstances that call for a quick commencement of action, its potassium salt form is especially appropriate (Wallace *et al.,* 2006).

Examples of diclofenac potassium brands in the market are Cataflam® 50 mg and Voltaren® 50 mg, Pregnancare supplement, etc.

1.7.1. Chemical and physical properties of diclofenac potassium

i. Chemical name: 2-[(2,6-dichlorophenyl) amino] benzene acetic acid monopotassium salt.
ii. Molecular formula: $C_{14}H_{10}C_{l2}KNO_2$.
iii. Molecular weight: ~334.2 g/mol.
iv. Solubility: Highly water-soluble due to the potassium salt.
v. Formulations: Available as oral tablets, capsules, and soluble powders.
vi. Wavelength of maximum absorbance in phosphate buffer: 276nm (Peretz *et al.,* 2004).

The structure of diclofenac potassium is shown below.

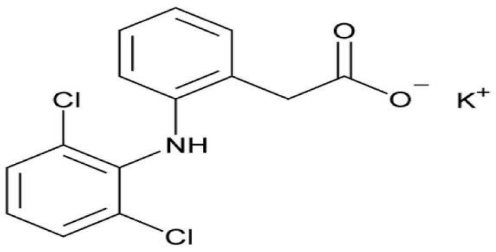

Figure 1.1: Chemical structure of diclofenac potassium (PubChem.org, 2025).

1.8. Mechanism of action of diclofenac potassium

It functions by inhibiting the enzymes known as cyclooxygenase (COX) specifically COX-1 and COX-2, lowering prostaglandin production which is a mediator of fever, inflammation, and discomfort. Diclofenac potassium reduces inflammation, discomfort, and high body temperature by focusing on these routes (Sinatra, 2009).

Uses of diclofenac potassium

- Severe pain: Pain following surgery, such as orthopedic or dental procedures, cramping during menstruation, or dysmenorrhea.
- Prolonged inflammatory disorders such as osteoarthritis, spondylitis ankylosing.
- Migraines: Because of its quick absorption, it works particularly well for acute treatment.
- Additional pain syndromes such as low back ache, sports-related injuries and musculoskeletal pain (De Barros *et al.,* 2015).

1.9. Pharmacokinetics

i. Absorption: Quickly taken up from the digestive system, reaching its maximum plasma concentration in 30 to 60 minutes.

ii. Distribution: Mostly (~99.7%) bound to plasma proteins, especially albumin.

iii. Metabolism: Mainly converted into hydroxylated forms in the liver by CYP2C9, which are then coupled with glucuronic acid.

iv. Excretion: Approximately 35% is excreted in bile and 65% in urine. With a half-life of 1-2 hours, it has a quick onset but requires several daily dosages for long-lasting effects (Chen *et al.,* 2014).

1.9.1. Administration and dosage

Depending on the patient's tolerance and the severity of the ailment, the usual dosage is 25 – 50 mg every 8 hours. To reduce gastrointestinal adverse effects, it is recommended to take it with food or milk. Extended-release formulations should not be chewed or crushed (Azzopardi, 2007).

1.10. Contraindications

i. Hypersensitivity to diclofenac or other NSAIDs
ii. Gastrointestinal conditions such as peptic ulcers, bleeding, or perforation (Azzopardi, 2007).
iii. Severe impairment of the liver or kidneys.
iv. Individuals who have recently experienced a myocardial infarction or stroke are at cardiovascular risk (Shaw *et al.,* 2000).

1.11. Adverse reactions associated with diclofenac

Typical adverse effects include dyspepsia, nausea, dizziness, headache, constipation, diarrhea (Shaw *et al.,* 2000).

Serious Adverse Reactions include ulcers or bleeding in the stomach, hepatotoxicity. Long-term use-related cardiovascular events such as a heart attack or stroke, reactions to hypersensitivity.

1.12. Advantages of the potassium salt form

i. Quick start of action: quicker absorption and dissolution than the sodium salt version.

ii. Beneficial for severe pain: Ideal for ailments requiring quick treatment, such as headaches and dysmenorrhea.

iii. Reduced chance of side effects associated with sodium: Which is advantageous for individuals with hypertension or other sodium-sensitive conditions (Fini *et al.,* 2005).

As a potent NSAID with a quick onset of action, diclofenac potassium is a great option for controlling inflammation and managing acute pain. To reduce any potential negative effects and guarantee safety, especially in vulnerable populations.

1.13. Vegetable oils

Vegetable oils, also known as vegetable fats, are triglyceride-rich oils derived from edible plant seeds or other parts (Alfred, 2005). Examples of seed oils, or fats derived from seeds, are cocoa butter, soybean oil, grape seed oil, and castor oil. Other plant-based fats include rice bran oil, olive oil, and palm oil (Parwez, 2007). Vegetable oil, as it is commonly used, can only relate to liquid vegetable fats at room temperature (Robin, 1999). Most vegetable oils are edible.

Vegetable oils should not be confused with essential oils. While vegetable oils are typically derived from seeds, nuts and fruits of plants, essential oils are typically derived from leaves, roots, flowers, stem, barks of plants by different extraction methods. Also, the main uses of vegetable oils are for their nutritional and moisturizing characteristics, whereas essential oils are prized for their medicinal and fragrant features. An example of a vegetable oil is castor oil (Biermann *et al.,* 2011).

1.13.1. Castor oil

Vegetable oil extracted from castor beans is known as castor oil (Alfred, 2005). It is a clear, colorless or light yellow liquid with a peculiar flavor and smell. Its density is 0.961 g/cm3, and

its boiling point is 313 °C (595 °F) (Aldrich, 2003). About 90% of the fatty acids in this mixture of triglycerides are ricinoleates. Other important ingredients are oleic and linoleic acids. It is used in the production of Soaps, lubricants, braking and hydraulic fluids, paints, dyes, coatings, inks, cold-resistant polymers, waxes and polishes, nylon, and fragrances (Mutlu *et al*., 2010).

Figure 1.2: Photograph of (A: *Castor seeds*, B: *Processed castor oil)* (Mutlu *et al.,* 2010).

1.14. An overview of hydroxylpropyl methylcellulose (HPMC)

HPMC is also known as hypromellose (de Silva *et al.,* 2005). It is a semisynthetic polymer primarily used as an excipient. It is inert and viscoelastic (Williams *et al.,* 2001). It is a solid that may be shaped into granules and has an appearance that ranges from slightly off-white to beige powder. When the substance dissolves in water, colloids are created. This non-toxic component can react violently with oxidizing substances and is flammable (Williams *et al.,* 2001).

1.14.1. Uses of HPMC

i. It is used in making tile adhesives
ii. HPMC finds applications as cement renders
iii. They are also seen in gypsum products
iv. They are widely used in Pharmaceutical production as bioadhesives (Nokhodchi *et al.,* 2012).
v. Due to their adhesive and colloidal nature, they find applications in paints and coatings
vi. They are used in making cosmetics
vii. They can also be used a detergents and cleaners
viii. Due to their ability to absorb water and swell that are used in the production of eye drops and contact lens
ix. They useful in the manufacture of polyvinyl Chloride (Koroloff *et al.,* 2004).

1.15. An overview of the skin structure

There are different layers in the skin, and keratinocytes make up the majority of the epidermis. Dermo-epidermal junction, or basement membrane, is the layer that lies beneath the epidermis. Securing the epidermis to the dermis is the function of this thin, multilayered structure. There is a greater concentration of fat in the hypodermis, which is located beneath the dermis. The skin is generally organized in part by the structures that have been described as shown in Figure 1.3 below.

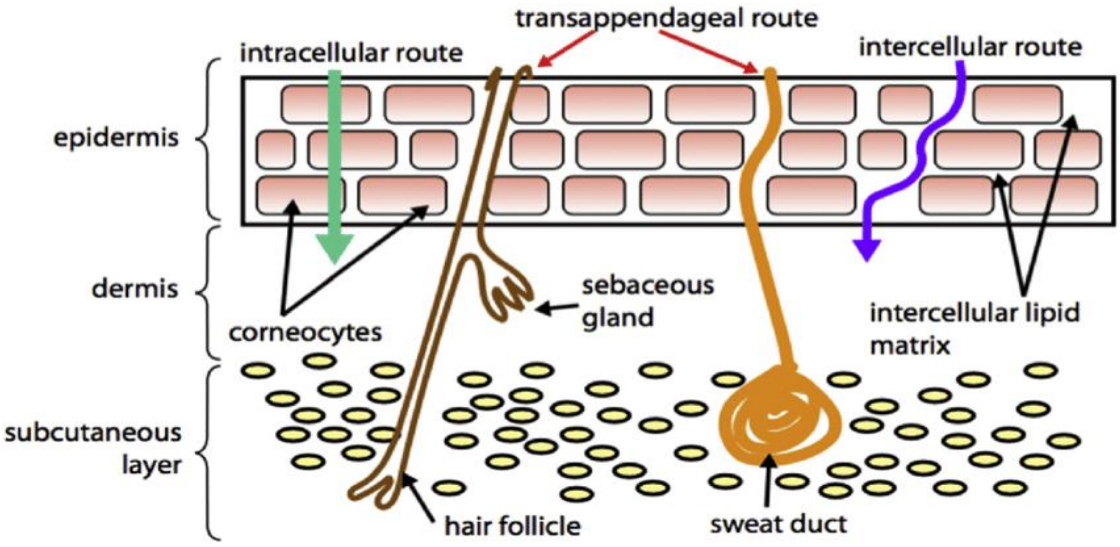

Figure 1.3: Schematic representation of the skin showing the different layers and routes of drug diffusion when administered through skin (Jain *et al*., 2016).

1.16. How drug permeate the skin

Diffusion via the intact epidermis and skin appendages, such as sweat glands and hair follicles, which form shunt routes, are the two main ways that drugs penetrate the skin. Because the intact epidermis makes up only 0.1% of the total human skin, drug penetration is hindered, mainly by the stratum corneum. The intercellular route and the transcellular route are the two recognized routes that pass through the intact barrier (Michaels *et al.,* 1975). This is illustrated in figure 1.3 above.

1.16.1. Major layer of the skin

i. Epidermis
ii. Dermis
iii. Hypodermis

1.16.1.1. Epidermis

The epidermis, which is the skin's outermost layer, is a stratified squamous epithelium mainly made up of keratinocytes at different stages of development. The primary cells in the epidermis that produce the keratin protein are called keratinocytes. Because it is avascular (without blood vessels), the epidermis depends on the dermis underneath it for waste elimination and nourishment delivery via the basement membrane. Keratinocytes are the major component of the epidermis as they make up to 95% (McGrath *et al.,* 2004).

Moving from the outermost later to the inner layer, the epidermis can be further divided into;

Stratum corneum

Stratum lucidum (only in palms and soles)

Stratum granulosum

Stratum spinosum

Stratum basale (also called the stratum germinativum) (Betts *et al.,* 2022).

The epidermis is not covered in blood vessels, instead, blood capillaries that reach the higher layers of the dermis diffuse blood to nourish the cells there.

1.16.1.2. Dermis

The layer of skin below the epidermis, known as the dermis, is made up of connective tissue and protects the body from pressure. The extracellular matrix of the dermis, which is made up of collagen fibrils, microfibrils, and elastic fibers embedded in hyaluronan and proteoglycans, gives the skin its tensile strength and elasticity (Breitkreutz *et al.,* 2009).

It is believed that germinative cells found in the dermis and subcutaneous tissues are responsible for the development of horns, osteoderm, and other extra-skeletal structures in animals (Smith *et*

al., 2015). The papillary region, which is the superficial area next to the epidermis, and the reticular region, which is the deeper, thicker area, are the two structural divisions of the dermis, which is intimately attached to the epidermis through a foundation membrane (Nasoori *et al.,* 2020).

1.16.1.3. Hypodermis

Just beneath the dermis is the subcutaneous tissue, sometimes referred to as the hypodermis. In addition to providing the skin with blood arteries and nerves, its function is to adhere the skin to the underlying bone and muscle. Slack connective tissue and elastin make up this structure. Fistulas, macrophages, and adipocytes are the principal cell types (fifty percent of body fat is found in the subcutaneous tissue). Body fat provides insulation and cushioning. Surface microbes invade the skin, including Staphylococcus epidermis. Each skin location has a different density of skin flora. Deeper hair follicle, gut, and urogenital entrance locations repopulate with germs that enter the cleaned skin surface (da Cunha *et al.,* 2017).

1.16.2. Intercellular route

Corneocytes, or the cells that make up the stratum corneum, are connected by this channel. Less organized lipids with more flexible hydrophobic chains can be found in the stratum corneum's interlamellar areas, including linker regions. As a result, the outer membranes of nearby cells and crystalline lipid lamellae have non-planar gaps. The trans-epidermal diffusion of lipidic and amphiphilic compounds depends on fluid lipids in the skin barrier. Taking advantage of the gaps between lamellae and corneocyte outer membranes, these molecules insert and move through intercellular lipid layers. While polar molecules can exploit the open space between a lamella

and a corneocyte outer membrane, hydrophilic molecules primarily diffuse laterally along surfaces of water-filled inter-lamellar spaces or through such volumes (Scheuplein *et al.,* 1971).

1.16.3. Transcellular route

This path goes through the lipids that act as an intermediary layer and corneocytes. Rich in keratin, the internal macromolecular matrix of the stratum corneum enhances mechanical stability without directly influencing the skin's diffusive barrier. Transdermal medication delivery is thought to be largely unaffected by transcellular diffusion. Understanding these pathways is essential to comprehending how drugs are delivered through the skin, with the stratum corneum playing a key role in restricting drug penetration. Transdermal drug distribution relies heavily on the interaction of hydrophobic and hydrophilic molecules and how they move through the intricate structure of the skin's outermost layer (Scheuplein *et al.,* 1971).

1.17. Overview of transdermal patch

A transdermal patch is a drug delivery system that helps to regulate the release of medication through the skin into the bloodstream over time (Cawello *et al.,* 2011).

An exact quantity of medication can be injected into the bloodstream through the skin using a transdermal patch. Transdermal patch devices were first approved by the FDA in 1981. Products with scopolamine (hyoscine) for motion sickness, nitroglycerin and clonidine for cardiovascular illness, fentanyl for chronic pain, and nicotine for smoking cessation are currently included in transdermal administration systems. Compared to oral and conventional injectable approaches, this drug delivery strategy offers advantages in terms of regulated and consistent dosing (Gaur *et al.,* 2009).

In the international market, transdermal devices such as Transderm Nitro (Ciba Geigy) and Nitrodisc (Searle) are examples. Others include Schwarz and Nitro Drug (Key Pharmaceuticals) and Deponit (Schwarz). These glyceryl trinitrate systems are used in the management of angina, each supply therapeutic concentrations of the medication in the blood for a full day. An example of a transdermal patch in the local market is Salonpass®

1.18. Mechanism of transdermal delivery system

For Transdermal Drug Delivery (TDD) systems to be developed successfully, it is essential to understand the kinetics of skin permeation. Percutaneous absorption, or the penetration of substances into various layers of the skin and their subsequent permeation across the skin into the systemic circulation, is a critical stage in the assessment of any type of TDD (Aulton 2002; Dhote 2012; Chandrasekaran *et al.,* 1978).

Molecules are absorbed through the skin in a sequential manner which include:

1.18.1. Penetration

This is the first stage of a material entering a certain layer of skin, usually the stratum corneum, which is the outermost layer. In addition to acting as a barrier of defense, the stratum corneum is essential in determining whether or not further penetration will be successful.

1.18.2. Partitioning

from the stratum corneum into the aqueous viable epidermis. Once the material has penetrated the stratum corneum, it must go into the viable epidermis, which is composed of areas with water. The material is being partitioned from the lipid-rich stratum corneum into the viable epidermis's watery environment during this phase.

1.18.3. Diffusion

Through the viable epidermis and into the upper dermis

At this point, the material permeates the layer of viable epidermis, which is a layer of living tissue located underneath the stratum corneum. During this diffusion phase, the chemical penetrates deeper into the epidermis and targets the higher dermis.

1.18.4. Permeation

As the material moves from one layer to another, permeation takes place.

Moving from a layer that is physically and functionally distinct from the first layer is part of this transition. The material is getting past the several epidermal layers and their unique properties.

1.18.5. Absorption

The drug's absorption into the systemic circulation is the last phase. The

material enters the bloodstream after passing through the layers of skin, where it is then dispersed throughout the body. The process of percutaneous absorption is finished by this systemic absorption (Ruela *et al.,* 2016).

1.19. Types of transdermal drug delivery system

Transdermal patches come in many different forms, each with its own method of delivering medication (Jyothika *et al.,* 2022). These four primary categories show the variety of choices available in the market.

1.19.1. Adhesive type

In this case, the stratum corneum acts as a barrier to regulate the release rate while the medication is incorporated directly in the adhesive. The Deponit nitroglycerin-releasing system, created in Europe by PharmaSchwartz/Lohmann, is a prime example (Shokri *et al.,* 2013).

1.19.2. Reservoir type

This kind contains the medication inside a reservoir that is frequently membrane-lined. This membrane, which could serve as a rate-controlling component, is coated with adhesive. The Nitrodisc nitroglycerin-releasing mechanism manufactured by Searle is one such (Yamagishi *et al.,* 2009).

1.19.3. Multi-laminate type

It is known for its intricate construction, which consists of several layers: a backing membrane, a medication encased in adhesive, a rate-controlling membrane, and a second adhesive layer. Notable examples are the Ciba product Transderm-scop (scopolamine) and the Boehringer Ingelheim product Catapres-TTS (clonidine) (Guy et al, 1987).

1.19.4. Matrix type

The medicine is released in a zero-order way in this instance because it is incorporated in a polymer matrix. The patch's sticky layer is placed slightly inside and on the edge. A release liner, glue, medication in the matrix, and backing membrane are basic parts. One such product is Key's Nitro-dur nitroglycerin-releasing TDDS (Gupta *et al.,* 2009).

1.20. Components of a transdermal patch

A transdermal patch is made up of the following;

i. Polymer Matrix: The main structural element that regulates medication release is the polymer matrix. The polymer ought to be inexpensive, non-toxic, and chemically inert. Derivatives of cellulose, zein, gelatin, waxes, gums, and different synthetic polymers are some examples. The polymer used in this experiment was the HPMC which is an aqueous polymer.

ii. Drug: For medications with appropriate physical chemistry and pharmacology, such as those with a short half-life, a limited therapeutic window, or considerable first-pass metabolism (such as fentanyl, nitroglycerin, and insulin), the transdermal route is preferable.

iii. Enhancers of permeation: This helps to raise the permeability of the drug to attain greater therapeutic medication concentrations. These consist of two-component systems which are lipophilic solvents, and surface-active substances. A common example of permeation enhancer is polysorbate 80 (tween 80).

iv. Adhesive: Promotes increased permeability of the surface, which allows for higher therapeutic medication levels. Vinyl and polyethylene are examples of backing laminates that should have a low modulus or great flexibility.

v. Release liner: This layer shields the patch from storage and is taken off before application.

vi. plasticizers and solvents (Aggarwal *et al.,* 2009).

The figure below shows a sketchy components of a transdermal patch

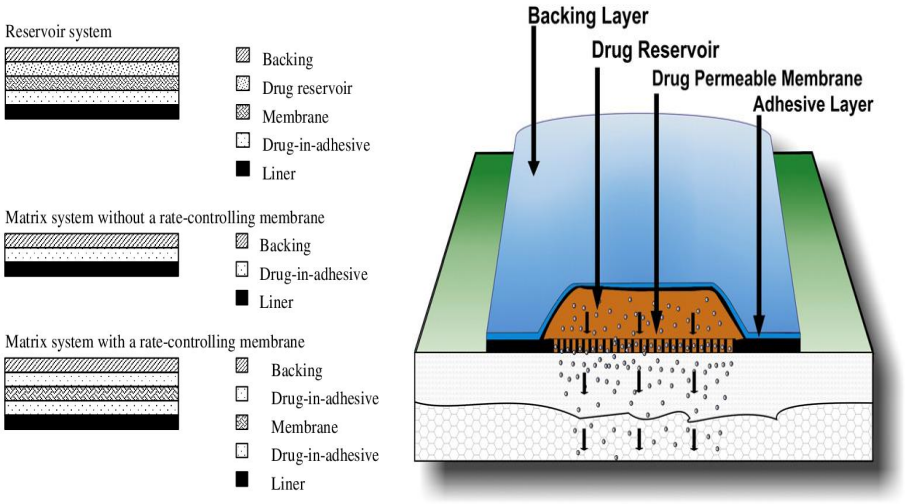

Figure 1.4 (A: schematic representation of a transdermal patch B: parts of a transdermal patch)

The average thickness of a transdermal patch is 0.3 mm thick (Kost *et al.,* 2000) and has progressively more medication in the innermost layer. The part that is closest to the skin has more drug than in the outermost layer.

1.21. Advantages of transdermal patch delivery system

i. Food consumption, intestinal transit time, and pH variations are only a few of the variables that are eliminated by the transdermal route regarding oral medication.

ii. Hepatic first-pass metabolic degradation is typically avoided by drugs administered via this route (Arhewoh *et al.,* 2005).

iii. Improved compliance: Patient compliance is now better. When issues occur during treatment, it is possible to quickly stop the transdermal device's medication delivery by removing it from the skin.

iv. Steady diclofenac release: An even and regulated medication release is typically achieved using this route.

v. The frequency and size of doses are reduced, which results in less negative effects basically because the patch's drug delivery rate is adjustable (Gaur *et al.,* 2009).

vi. Convenience: Avoidance of pain associated with needles and its non-invasive nature during administration (Gaikwad, 2013).

1.22. Challenges associated with transdermal drug delivery system

i. Skin permeability: Big molecules have a hard time effectively passing through the skin's natural barrier.

ii. Formulation stability: Throughout the course of the patch's planned shelf life, diclofenac must stay stable and effective.

iii. Allergies and irritation: There may be a chance of allergic responses or skin irritation at the application site.

iv. Variable absorption: The rate at which diclofenac is absorbed can be influenced by variations in skin thickness, moisture, and other personal characteristics.

The function of the skin's barrier changes with age, among individuals, even between areas on the same person (Gaikwad, 2013).

1.23. Factors influencing skin permeability

The greatest problem of transdermal drug delivery system is the physical barrier posed by the undamaged skin. Other contributing factors include:

Skin age: There are discernible variations in skin permeability between adults and younger people in relation to older people. Children show higher permeability due to their larger surface area per unit body weight, but they are also more vulnerable to harmful impacts. Notably, a number of drugs have been associated with serious adverse effects, including strong steroids, boric acid, and hexachlorophene. There are discernible variations in skin permeability between adults and younger people in relation to older people. Children show higher permeability due to their larger surface area per unit body weight, but they are also more vulnerable to harmful impacts (Todo, 2017).

1.23.1. Environmental factors such as:

i. Sunlight: Exposure to sunlight can lead to bruises due to thinning blood vessel walls and pigmentation changes such as solar lentigines or freckles (Fang *et al.,* 2006).
ii. Cold seasons: Dry, irritated skin is a common result of the winter season. In response to the weather-induced dryness, the skin produces more oil. Using moisturizers and drinking enough water can help reduce the signs of dry skin (Fang *et al.,* 2006).
iii. Air pollution: The natural defense mechanism of the skin might be hampered by dust and invisible chemical contaminants in the air. This interference could affect how well drugs are delivered through the skin and cause acne or patches (Fang *et al.,* 2006).

1.23.2. Physicochemical factors such as;

i. Temperature of skin: The diffusion coefficient is directly proportional to the temperature. In other words, the impact of temperature varies penetration rate (Aulton *et al.,* 2013).

ii. pH of skin: Molecule transit is influenced by the pH of the skin; only unionized molecules may flow through the lipid membrane with ease. The effective membrane gradient is impacted by the different degrees of dissociation that weak acids and bases experience based on their pH and pKa or pKb values (Aulton *et al.,* 2013).

iii. Hydration: Softening of skin will lead to increased permeability of the skin and consequently increase in drug penetration (Aulton *et al.,* 2013).

1.24. Technological innovations

In order to overcome these challenges, technological innovations such as

i. The use of micro needles to create micro-channels in the skin to aid permeation

ii. The use of chemical enhancers to temporarily disrupt the skins barrier to aid permeation

iii. Iontophoresis which uses current to drive diclofenac into the skin

iv. Sonophoresis which involves the use of sound to permeate the skin are being researched.

InsuPad, InsuJet, and Zosano Pharma are some of the companies and research institutions actively working on transdermal patches (Halimi *et al.,* 2014).

1.25. Evaluation of transdermal patches

The following evaluations were carried out to test the integrity of the patches.

1. *Dimensions*: This was done so as to evaluate batch consistency in terms of thickness and weight which largely affect the rate of release from the patch. Having varying thickness will produce variations in results so it is important the thickness remains constant.

2. *Folding endurance*: As most transdermal patches are rotated through administration sites such as the back, flank, upper arm and chest the patch must possess some levels of endurance when it experienced folding especially when placed at various joints.

3. *Bioadhesion test*: The test was used to check for how well the transdermal patch can adhere to the skin. A good adhesion character is required. The excised skin of a rat was used in this evaluation.

4. *Drug content*: This was done to check the drug content uniformity of the patch.

1.25.1. In vitro studies

This study was done to demonstrate the release profile of the patches in a physiological environment that mimic the pH of the body. Batches which showed a good release were selected for *ex vivo* studies.

1.25.2. Ex vivo studies

This study was carried out using highly vascularized excised rat skin. This was to assess the diclofenac delivery profile across skin.

1.26. Significance of study

This study is significant in addressing the challenge of managing pain and inflammation in athletes, particularly those with ankle injuries, while taking into account any underlying comorbidities, such as asthma or peptic ulcer disease. Current treatments for pain relief, such as oral nonsteroidal anti-inflammatory drugs (NSAIDs) like diclofenac potassium, often present risks like gastrointestinal irritation or complications in individuals with asthma. Transdermal

delivery of diclofenac potassium offers the advantage of bypassing the gastrointestinal tract, thus reducing the potential for adverse effects. Additionally, this delivery method ensures a controlled and sustained release of the drug, enhancing compliance and allowing athletes to continue their performance with minimal disruption. By utilizing a fast-onset transdermal patch, this research could help improve rehabilitation outcomes for athletes, enabling them to return to their sports more quickly, while managing pain effectively without compromising their health. Also, a decrease in the dosing frequency of diclofenac potassium and the promotion in the utilization of cellulose as it is a common polymer in our environment is encouraged by this study.

1.27. Expected outcomes

i. Patches with high bioadhesion
ii. Patches with better drug release
iii. Production of durable patches
iv. Reduced frequency of diclofenac potassium dosing consequently minimizing systemic side effects

1.28. Aims and Objectives

The aim of this study is to investigate how the incorporation and variation of castor oil affects diclofenac potassium transdermal films.

The specific objectives are to;

i. Assess physicochemical properties of the patches such as weight, thickness, drug content
ii. Test for the pharmaceutical outcome of the transdermal patches e.g. bioadhesion, folding endurance, and drug release
iii. Assess *in vitro* and *ex vivo* drug release profile.

CHAPTER TWO

Materials and Methods

2.1. Materials

The following materials were used as received

i. Diclofenac potassium obtained as a gift from JSP Pharma Company Limited

ii. Polysorbate 80 (as tween 80) obtained from PARK Scientific Limited, Northampton, UK.

iii. HPMC obtained from PARK Scientific Limited, Northampton, UK.

iv. Castor oil obtained from PARK Scientific Limited, Northampton, UK.

2.2 Method

The patches were made by the solvent casting technique as also used by Rajwant *et al.,* 2022. Hydroxylpropyl methylcellulose served as the aqueous base in a micro emulsion of castor oil which served as the vehicle containing diclofenac potassium.

2.2.1 Preparation of diclofenac patches

The formula for the preparation of the transdermal patches is shown in Table 2.1 below. Six batches of the transdermal patches labelled, PQ0, PQ1, PQ2, PQ3, PO1, PO2, PO3 were prepared. 16 ml of distilled water containing 1.7g of HPMC was closely combined with 0.1g of diclofenac potassium. Next, 0.2 ml of Tween 80 and 0.3 ml of castor oil were added, and the mixture was agitated for approximately five minutes. The PQ3 batch of patches was created by pouring the slurry into a petri dish and letting it air dry for 48 hours. The air-dried patches were divided into ten (10) 1x1cm^2 sections

Table 2.1: Formula for the preparation of the batches of diclofenac transdermal patches (TDP)

Batches	Diclofenac (g)	Tween 80 (ml)	HPMC (g)	Castor oil (ml)
PQ0	0.1	0.2	2.0	-
PQ1	0.1	0.2	1.9	0.1
PQ2	0.1	0.2	1.8	0.2
PQ3	0.1	0.2	1.7	0.3
PO1	0.1	0.2	1.9	0.1
PO2	0.1	0.2	1.8	0.2
PO3	0.1	0.2	1.7	0.3

HPMC=Hydroxylpropyl methylcellulose

PQ= drug dispersed in aqueous phase

PO= drug dispersed with oily phase

2.2.2. Evaluation of transdermal patches

i. Dimensions

This was done to evaluate batch consistency. A digital balance was used to weigh each of the ten 1 x 1cm^2 patches from each batch, and the average weight of the 10 patches was computed and noted. Using a micrometer screw gauge, the thickness of the several batches of patches was measured at various points on the patch's surface, and the average thickness was recorded.

ii. Folding endurance

Method used to measure this was folding and opening the patches repeatedly at the same location until they were cracked or broken; the results were expressed as the number of folds.

iii. Bioadhesion test: The test is used to check for how well the transdermal patch can adhere to the skin.

Every batch of patches underwent this test using an adjusted variant of Attama *et al.'s* methodology. A burette secured to a retort stand makes up the equipment. A glass slide was positioned at a 30° angle using a wooden support. Rat skin that had been excised and treated was adhered to a glass slide, and the patch was applied to the skin's exposed surface for fifteen minutes in order to facilitate polymer contact and hydration. Water was poured into the burette and applied to the skin patch at a constant flow rate of 2 ml/sec until the patch separated from the removed rat skin. The mass flow rate of water (g/sec) was then used as a measure of bioadhesion using the mass conversation formula shown in equation 1.;

$$\underline{Density}/Volume \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

iv. Drug content: This was done to check the content uniformity of the patch.

Each batch's patch was cut into small pieces and put in a petri dish with 10 ml of phosphate buffer solution (pH 6.8). The dish's contents were shaken periodically until the patches completely disintegrated. One milliliter of this solution was then further diluted in 9 ml of the phosphate buffer solution and the mixture was then analyzed spectrophotometrically at λmax of 276 nm using a T70 PG Instrument Ltd, USA in the department of Pharmaceutical Chemistry, University of Benin, Benin City.

2.2.3. In vitro studies

Patches were selected at random from each batch. Each batch's patch was cut into small pieces and one side of the patch was covered with a broken petri dish with the aid of a glue. This was then put in a 500 ml - capacity dissolution machine containing phosphate buffer solution (pH 6.8). Ten milliliter of this solution was then withdrawn at intervals of 0, 5, 10, 20, 30, 40, 50, and 60 minutes. The solution was then analyzed spectrophotometrically at λmax of 276 nm using a T70 PG Instrument Ltd, USA in the department of Pharmaceutical Chemistry, University of Benin, Benin City. Batches that gave a good release profile were then selected for the study of *ex vivo* release across the skin

2.2.4. Ex vivo studies

A highly vascularized dorsal slice of an adult rat's skin was used for this investigation. The area was defatted by soaking in acetone for one hour after being soaked in 5% NaOH for thirty

minutes to remove the hair from the skin. It was immersed in normal saline after defatting. Forming the donor unit, the patches were firmly placed on the rat skin. A dissolving device serving as the receptor compartment was filled with 500 ml of phosphate buffer solution pH 6.8, kept at 32 ± 0.5 ºC, and agitated at 50 rpm before the donor unit was placed within the basket unit.

Aliquots of 5 ml of sample were withdrawn from the receptor compartment at hourly intervals up to 6 hours, while replacing with equal volume of the receptor medium. Withdrawn samples were then analyzed spectrophotometrically at 276 nm.

CHAPTER THREE

RESULTS AND DISCUSSION

3.1. Weight Uniformity of the transdermal patches

The weight uniformity evaluation of diclofenac TDP showed mean weights ranging from 1.92 to 2.79 g as shown in Table 3.1.

Table 3.1: Some physicochemical parameters of diclofenac transdermal patches

Parameters	PQ0	PQ1	PQ2	PQ3	PO1	PO2	PO3
Weight (g±SD)	2.47±0.43	2.43±0.46	2.41±0.45	1.92±0.32	2.79±0.52	2.33±0.41	2.41±0.45
Thickness (mm±SD)	0.37±0.18	0.51±0.03	0.46±0.27	0.49±0.03	0.37±0.18	0.56±0.09	0.60±0.05
Folding Endurance (n±SD)	480±30	301±10.40	403±5.50	265±13.20	350±30	80±13	261±30.10
Drug Content (%)	77	87	85	83	65	60	77
Bioadhesion (g/sec±SD)	3.60±0.23	1.90±0.10	1.76±0.17	1.35±0.09	2.90±0.13	1.40±0.25	1.36±0.28

Key:

PQ0 is the batch without oil. That is, blank
PQ1 is the batch with 5% oil where the drug was dispersed in the aqueous phase
PQ2 is the batch with 10% oil where the drug was dispersed in the aqueous phase
PQ3 is the batch with 15% oil where the drug was dispersed in the aqueous phase
PO1 is the batch with 5% oil where the drug was dispersed in the oily phase
PO2 is the batch with 10% oil where the drug was dispersed in the oily phase
PO3 is the batch with 15% oil where the drug was dispersed in the oily phase
SD stands for standard deviation

Weight of patches ranged between 1.92 to 2.79 g. The observed variability in weight could stem from limitations in the solvent casting process, including non-uniform spreading of the formulation and inconsistencies in drying. To avoid this limitation in the industries, patches are often dried in-between foils. This will help to achieve uniformity in drying and thickness. While the deviations were within the acceptable range (The USP suggests a deviation of not more than ±5 – 10%), optimization of process parameters is necessary to minimize variations (Chandrasekaran *et al.,* 1978) This uniformity is critical for ensuring consistent drug delivery and therapeutic efficacy, especially for diclofenac potassium patches intended for sensitive patient populations like those with asthma or peptic ulcers.

3.2. Thickness

The thickness evaluation of the transdermal patches demonstrated mean values ranging from 0.37 to 0.60 mm. While some batches such as 0.51 and 0.49 mm showed consistent thickness values, others, like 0.46 mm, exhibited significant variability. This variability could be attributed to the same factors that affected the weights; the solvent casting technique, particularly uneven solution spreading and drying conditions. Batches which shrank significantly were observed to be thicker than those that remained flat throughout the drying process. Variations in thickness are of concern as they may influence the uniformity of drug distribution and release rates. Optimization of the casting and drying processes is essential to minimize these discrepancies and enhance batch-to-batch consistency (Hai *et al.,* 2008).

3.3. Folding Endurance

Folding endurance results suggest variability in the mechanical strength and durability of transdermal patches. The folding endurance test revealed a significant variability across the patches, with values ranging from 80 to 388 folds. While most patches exhibited an acceptable range of 200–400 folds, one patch, PO2 demonstrated notably lower folding endurance (80 folds). This variation suggests potential inconsistencies during the solvent casting process such as incomplete drying or polymer formulation inconsistencies. A patch's folding endurance directly impacts its practical usability and longevity on the skin. Patches with insufficient folding endurance are more prone to cracking or tearing, which can compromise the controlled release of the drug and reduce the patch's effectiveness (Arhewoh *et al.,* 2005). Optimization of formulation parameters including plasticizer concentration and thickness are essential to enhance the mechanical properties and ensure consistent, reliable folding endurance.

3.4. Bioadhesion

The highest force observed (3.60 for the blank and 2.95 g/sec for an active patch) indicates a patch with strong bioadhesion, which is ideal for active athletes. It was observed that as the percentage oil increased, the bioadhesion decreased. Therefore, the amount of oil may greatly impact bioadhesion. Athletes such as football players who engage in intense movements, require patches that remain securely in place under various conditions, including perspiration. Strong adhesion (2.95 g/sec) ensures that the patch remains affixed throughout physical activity, which maximizes the time the diclofenac potassium is in contact with the skin, enhancing the absorption and effectiveness of the drug. This strong adhesion is particularly valuable in the context of managing ankle injuries in athletes, as prolonged delivery of the anti-inflammatory

drug can help reduce pain and inflammation, improving recovery time and performance on the field. Adhesion forces in the range of 1.57 g/sec to 1.41 g/sec represent moderate adhesion strength. These patches might still stay on the skin, but there could be concerns under more demanding conditions, such as extended periods of physical activity or sweating. Moderate adhesion might not be ideal for high-intensity sports, where patches could risk detaching prematurely. For football players, ensuring that the patch does not detach unexpectedly is critical, particularly if they are actively participating in intense matches or training sessions. If the bioadhesion of these formulations isn't optimized, there could be insufficient skin contact, leading to inconsistent drug delivery or the need for frequent reapplication. The lower end of the results (1.33 to 1.25 g/sec) indicates weak bioadhesion. These values could suggest that the patch may not stay adhered effectively, particularly during physical activity like running, kicking, or sudden movement, where dynamic forces may dislodge the patch (Almazan et al., 2020).

3.5. Drug content

The drug content analysis of the diclofenac potassium transdermal patches across seven batches showed a range of percentages, highlighting variability in the uniformity of drug distribution. The drug content values exhibit considerable variability, with the highest content observed in Batch 3 (83%) and the lowest in batch 1 (58%). This variability suggests that the production method may have inconsistencies in critical steps such as solvent evaporation, or polymer matrix distribution. Also, inconsistent stirring during the preparation phase might have resulted in unequal drug dispersion throughout the matrix. While batches PQ2, PO1, and PO3 approached the upper limit of acceptable uniformity, others like Batch PQ1 (58%) and Batch PO2 (60%) fell

below the typically recommended pharmaceutical range of ±10% variation from the intended drug content.

3.6. *In vitro* release

Results for the *in vitro* release profile is shown in Figure 3.1 below.

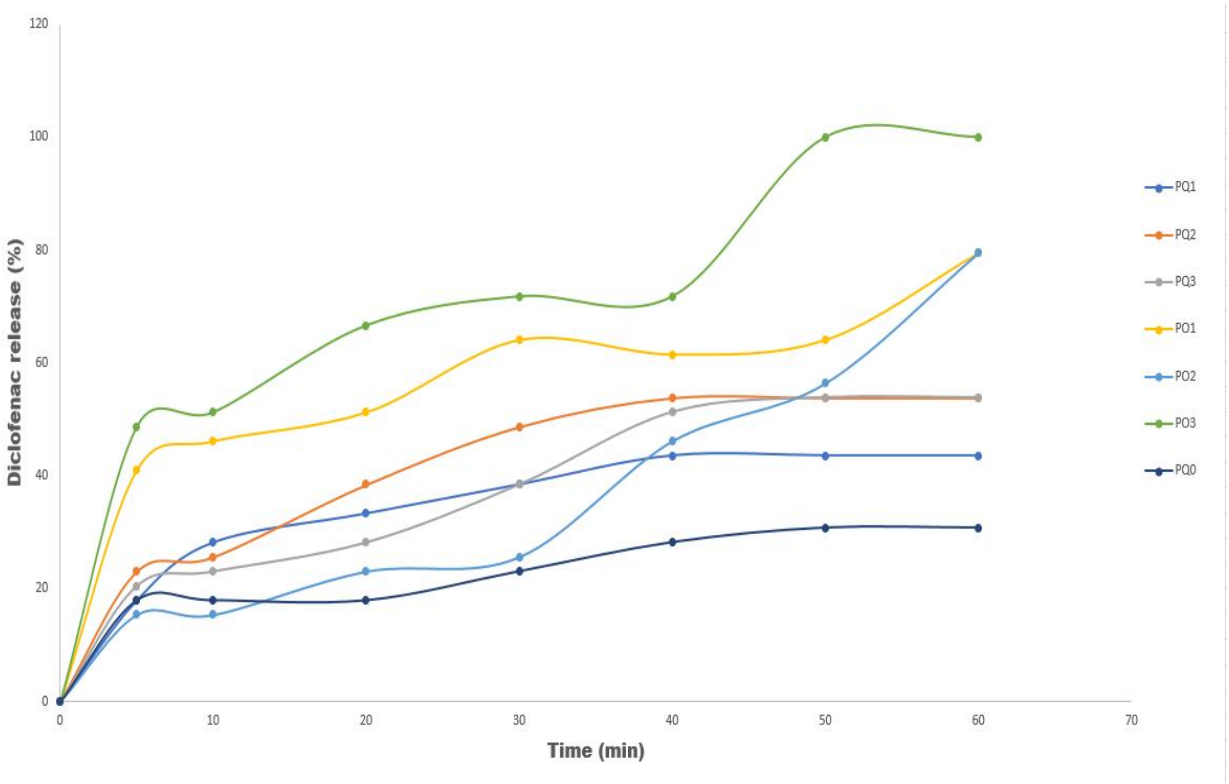

Figure 3.1. *In vitro* release result of diclofenac from TDP.

Key:

PQ0 is the batch without oil. That is, blank

PQ1 is the batch with 5% oil where the drug was dispersed in the aqueous phase

PQ2 is the batch with 10% oil where the drug was dispersed in the aqueous phase

PQ3 is the batch with 15% oil where the drug was dispersed in the aqueous phase

PO1 is the batch with 5% oil where the drug was dispersed in the oily phase

PO2 is the batch with 10% oil where the drug was dispersed in the oily phase

PO3 is the batch with 15% oil where the drug was dispersed in the oily phase

Batches PQ2 and PQ3 exhibited similar plateau release pattern, achieving cumulative drug release of 53 and 53.8%, respectively, within 60 minutes. This controlled and steady release profile could be advantageous for sustained drug delivery over time, but the relatively low percentage released suggests potential for optimization in enhancing the release rate for faster therapeutic effect. PQ0 displayed the slowest release, reaching 30% at 60 minutes. This slower release rate may be due to formulation factors such as absence of oil in the patch leading to suboptimal drug diffusion properties as also observed with PQ1. While suitable for prolonged delivery, the initial slower release might delay therapeutic onset. Batches PO1 and PO2 showed more rapid release, with PO1 reaching 79% and PO2 achieving 79.4% at 60 minutes. The burst release observed within the first 20 minutes indicates a fast onset of action, ideal for managing acute pain in athletes. However, the faster release may lead to shorter duration of sustained delivery. PO3 had the highest release rate, with a cumulative drug release of 100% at 60 minutes. This batch exhibited a pronounced burst release phase (24.6% within 5 minutes) followed by rapid but steady release. Such profiles are beneficial for immediate therapeutic effect but may require formulation adjustments to avoid excessive burst release. Importantly, the fast release profile in the batches with oily phase (PO) may be attributed to the fact that the drug is embedded in the oil and as such the drug is released alongside the oil. Unlike when the drug is dispersed in aqueous phase which when it has evaporated will leave the drug embedded in the HPMC base leading to a slow release profile.

The *in vitro* release results revealed varied drug release profiles, influenced by batch-specific formulation properties. All batches demonstrated an increase in drug release with time, highlighting the capability of the transdermal patches to release diclofenac potassium consistently. However, there were significant differences in release rates and cumulative amounts across batches, indicating formulation variability and distinct drug release dynamics.

3.7. *Ex vivo* release

Results obtained are shown in Figure 3.2 below.

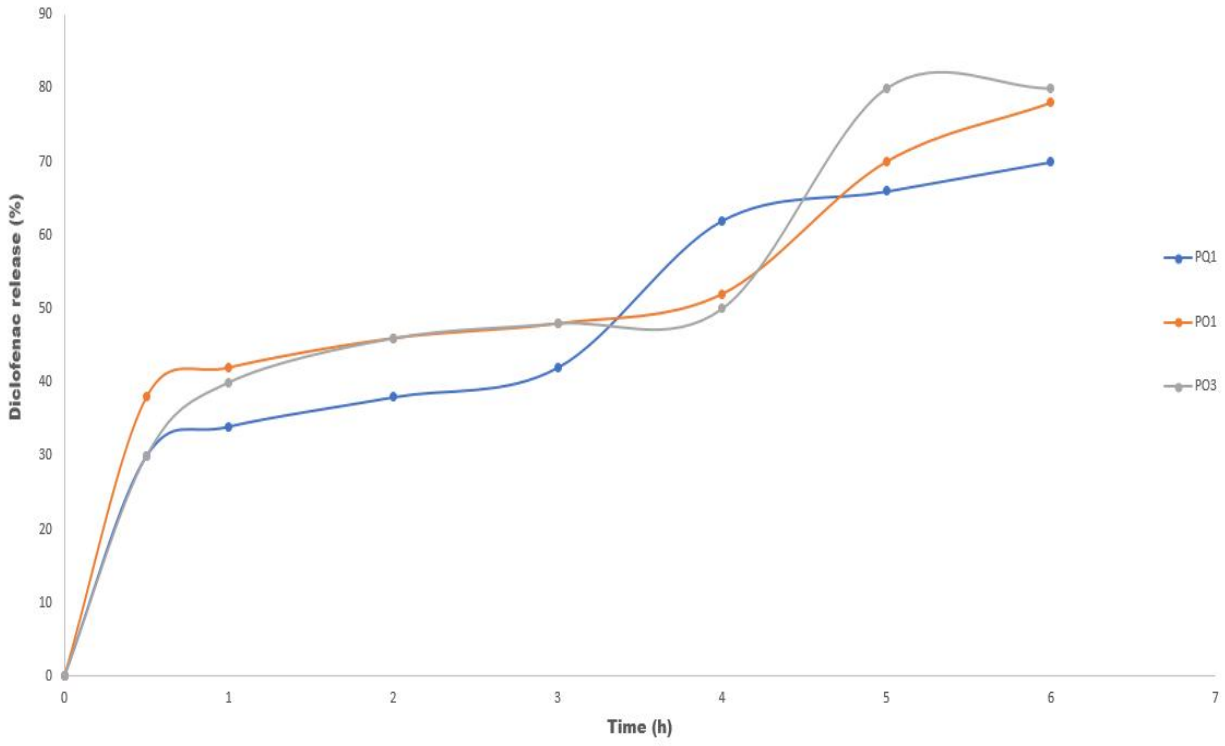

Figure 3.2: *Ex vivo* release of diclofenac from TDP across rat skin.

Key:

PQ1 is the batch with 5% oil where the drug was dispersed in the aqueous phase

PO1 is the batch with 5% oil where the drug was dispersed in the oily phase

PO3 is the batch with 15% oil where the drug was dispersed in the oily phase

All batches showed an increase in drug release over time, with the release plateauing in the later hours. Maximum cumulative release values ranged from 70 (PQ1) to 80% (PO3), suggesting variability in formulation efficiency or interaction with the skin membrane. Batch PQ1 demonstrated a slower release compared to the other two batches, with 70% of the drug released after 6 hours. The initial release at 0.5 hours (30%) was the lowest among the batches, indicating a more controlled release rate and a delayed onset of action. This slower and sustained release could benefit scenarios requiring prolonged drug delivery rather than immediate therapeutic effects. PO1 showed a moderate balance between rapid and sustained release, reaching 78% after 6 hours. The cumulative release at 0.5 hours (38%) indicates a faster onset compared to batch PQ1, while the steady increase over the following hours supports sustained delivery. This profile is well-suited for pain management where a quick onset is needed, followed by prolonged efficacy. Batch PO3 exhibited the highest drug release (80%) at 6 hours, with the most rapid release in the initial phases (30% at 0.5 hours and 40% at 1 hour).

This rapid release indicates potential for immediate therapeutic action, although it might lead to shorter duration of effect if not paired with sustained delivery mechanisms. The biological membrane's permeability influenced the drug release kinetics across batches. Batch PO1 showed faster initial release but PO3 showed the highest release, implying better permeability or reduced matrix-drug interaction, facilitating quicker diffusion into the biological membrane.

CHAPTER FOUR

Conclusions and recommendations

4.1. Conclusion

This study suggests that transdermal patches formulated by dispersing drug in the lowest percentage of oil possible (in this case, 5%) will give a good bioadhesion and a better release across skin. Batches with the minimum percentage of oil (5%) showed better bioadhesion. Diclofenac potassium transdermal patches developed in this project demonstrated a good release with the oily medium of dispersion. Drug dispersed in the oil (PO) showed a better release profile. Therefore, in the optimization of transdermal patches with intended high bioadhesion and fast drug release profile, the drug may be dispersed in oil instead of the aqueous phase and with the lowest percentage of oil possible.

4.2. Recommendation

There will be need for further *in vivo* studies to validate the efficacy and safety of the patches in real-life conditions. This will help to evaluate the patches under dynamic conditions such as sweating, mechanical stress, and extended duration (beyond 6 hours) to assess their practicality during sports activities. More so, advanced bioadhesives may be investigated to improve patch adherence during physical activity, ensuring that the patches remain securely attached under challenging conditions like movement and perspiration.

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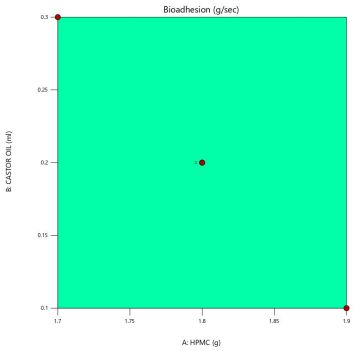
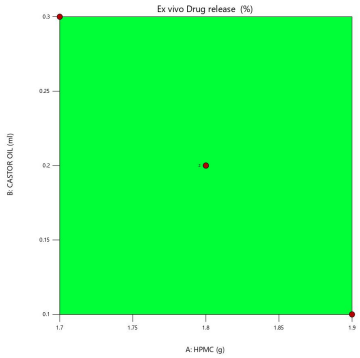
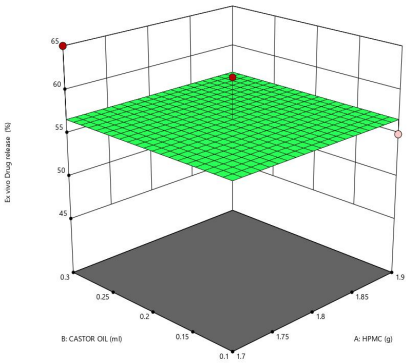
APPENDIX

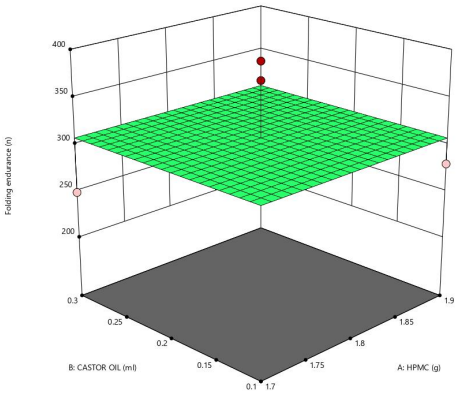




3D Surface

3D Surface





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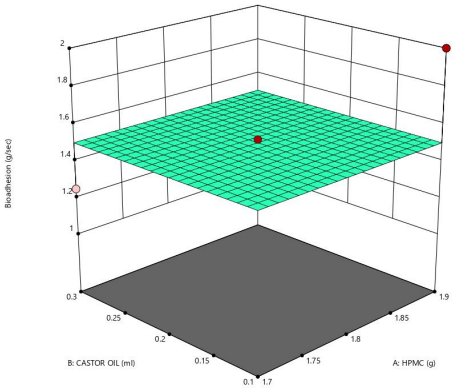
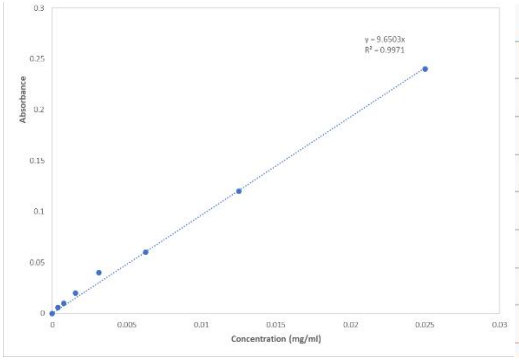




Time (min)	PQ1	PQ2	PQ3	PO1	PO2	PO3
0	0	0	0	0	0	0
5	0.007	0.009	0.008	0.016	0.006	0.019
10	0.011	0.01	0.009	0.018	0.006	0.02
20	0.013	0.015	0.011	0.02	0.009	0.026
30	0.015	0.019	0.015	0.025	0.01	0.028
40	0.017	0.021	0.02	0.024	0.018	0.028
50	0.017	0.021	0.021	0.025	0.22	0.039
60	0.017	0.021	0.021	0.031	0.26	0.039

Samples	Absorbance	Concentration (mg/ml)
A	0.46	0.1
B	0.24	0.025
C	0.12	0.0125
D	0.06	0.00625
E	0.04	0.003125
F	0.02	0.0015625
G	0.01	0.00078125
H	0.008	0.000390625
I	0.006	0.0019531325
J	0.005	0.00097656625
Stock = 1mg/ml		

EX VIVO ABSORBANCE

Time (h)	PQ1	PO1	PO3
0	0	0	0
0.5	0.015	0.025	0.028
1	0.017	0.031	0.039
2	0.028	0.032	0.04
3	0.03	0.033	0.045
4	0.031	0.035	0.043
5	0.032	0.038	0.045
6	0.032	0.041	0.05

THICKNESS OF BATCHES (mm)

Batches	I	II
PQ1	0.53	0.50
PQ2	0.16	0.49
PQ3	0.60	0.55
PO1	0.49	0.51
PO2	0.37	0.76
PO3	0.46	0.51

Batches	Content (mg/ml)
PQ0	0.0077
PQ1	0.0058
PQ2	0.0075
PQ3	0.0083
PO1	0.0065
PO2	0.0060
PO3	0.0077

Average drug content in each patch in 1ml is 0.007mg/ml

BIOADHESION RESULTS (g/sec)

Batches	Vol. of Water (ml)			Time of pull (sec)			Bioadhesion g/sec (weight of water/time of pull)		
	I	II	III	I	II	III	I	II	III
PQ0	400	450	405	120	120	109	3.33	3.75	3.71
PQ1	300	280	284	150	160	150	2	1.75	1.89
PQ2	284	280	250	180	150	165	1.57	1.86	1.51
PQ3	254	245	200	180	175	160	1.41	1.4	1.25
PO1	354	360	358	120	120	130	2.95	3	2.75
PO2	100	92	110	75	77	65	1.33	1.19	1.69
PO3	155	168	120	125	100	102	1.24	1.68	1.17

WEIGHTS OF BATCHES (g)

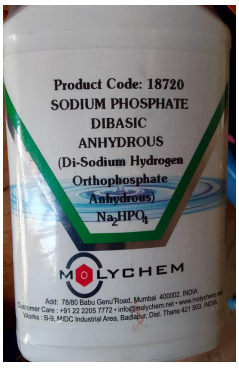
Batches	I	II	III
PQ0	2.00	2.85	2.56
PQ1	2.80	2.15	2.07
PQ2	3.27	2.90	2.21
PQ3	2.41	3.12	2.29
PO1	2.38	1.85	2.94
PO2	1.98	2.81	2.56
PO3	2.48	2.95	2.34

INDIVIDUAL WEIGHTS OF PATCHES (g)

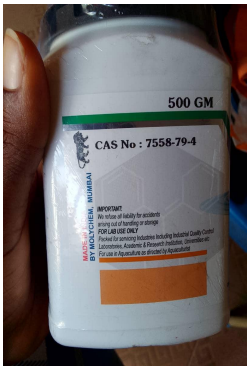
Batches	Weight
PQ0	0.08
PQ1	0.07
PQ2	0.09
PQ3	0.08
PO1	0.09
PO2	0.07
PO3	0.10

Average weight is 0.08g for each patch


Product Code: 18720
SODIUM PHOSPHATE
DIBASIC
ANHYDROUS
(Di-Sodium Hydrogen
Orthophosphate
Anhydrous)
Na_2HPO_4
MOLYCHEM


Product Code: 18720
SODIUM PHOSPHATE
DIBASIC
ANHYDROUS
(Di-Sodium Hydrogen
Orthophosphate
Anhydrous)
Na_2HPO_4
MOLYCHEM


500g
DESCRIPTION: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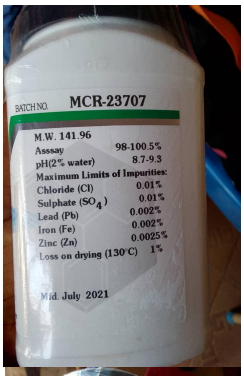
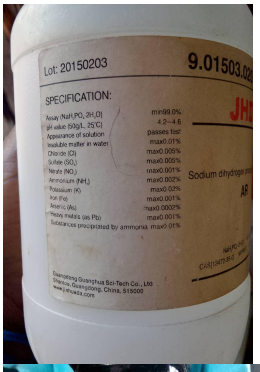

BATCH NO. MCR-23707
M.W. 141.96
Assay 98-100.5%
pH(2% water) 8.7-9.3
Maximum Limits of Impurities:
Chloride (Cl) 0.01%
Sulphate (SO_4) 0.01%
Lead (Pb) 0.002%
Iron (Fe) 0.002%
Zinc (Zn) 0.0025%
Loss on drying (130°C) 1%
Mfd. July 2021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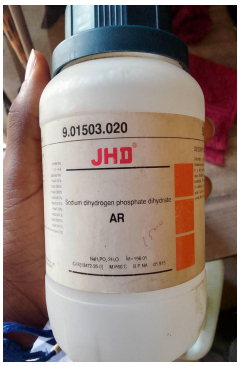
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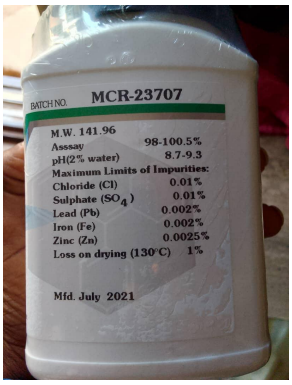
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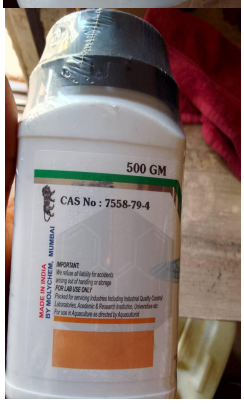
500 GM
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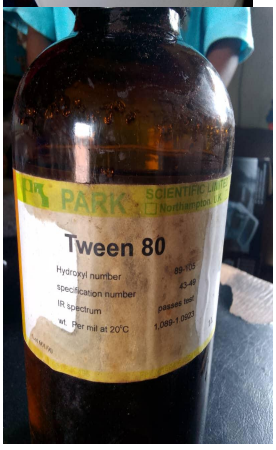
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Tween 80
Hydroxyl number
specification number
IR spectrum
wt. Per ml at 20°C