THE EFFECT OF A BLEND OF HYDROPHILIC POLYMERS ON DRUG RELEASE FROM DICLOFENAC MATRIX TABLET

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A PROJECT SUBMITTED TO THE DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL TECHNOLOGY IN PARTIAL FULFILMENT OF THE PHARMACY (PHARM.D) DEGREE OF THE UNIVERSITY OF BENIN, BENIN CITY,

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CERTIFICATION

This is to certify that this work was carried out by **EWOMAZINO ANITA OLOKOR,** in the Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Benin City, Edo State, Nigeria, in partial fulfillment for the award of the Pharm. D degree from the University.

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DEDICATION

This work is dedicated to everyone who believed in me, who encouraged and told me this educational pursuit was possible.

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ABSTRACT

Background: Diclofenac is a widely used non-steroidal anti-inflammatory drug (NSAID) prescribed for the management of pain and inflammatory disorders such as arthritis. Despite its therapeutic effectiveness, conventional immediate-release diclofenac formulations are often associated with frequent dosing and increased risk of gastrointestinal irritation due to rapid absorption and elimination. Sustained-release matrix tablet systems have been developed to address these limitations by providing prolonged drug action, reducing dosing frequency, and minimizing adverse effects. The selection and optimization of excipient blends, especially hydrophilic polymers, play a pivotal role in achieving a desirable sustained-release profile and robust tablet quality.

Objective: This study investigates the effect of polymer blends, specifically hydroxypropyl methylcellulose (HPMC) and maize starch mucilage, in combination with Eudragit RL-100 and polyethylene glycol (PEG), on the physical properties and drug release characteristics of sustained-release diclofenac sodium matrix tablets.

Method: Matrix tablets were manufactured by direct compression, utilizing varying proportions of HPMC and maize starch mucilage as hydrophilic polymer binders within systems also containing Eudragit RL-100 and PEG. All formulations were evaluated for tablet hardness, friability, and disintegration time using standardized pharmacopeial procedures, with an emphasis on comparing physical integrity and sustained-release performance across ten distinct batches.

Result: The results showed that tablets formulated with HPMC possessed higher hardness values (up to 6.88 ± 0.13 kg/cm²) and prolonged disintegration times (up to 394.33 ± 25.33 min),

whereas the substitution with maize starch mucilage led to reduced hardness (down to 3.20 ± 0.25 kg/cm²) and faster disintegration (as low as 25.60 ± 2.00 min). Friability values remained below 0.20% in all batches, demonstrating robust mechanical properties regardless of binder type. The transition from gel-controlled to swelling-erosion-controlled tablet matrices facilitated modulation of drug release rates in sustained-release formulations.

Conclusion: Blending hydrophilic polymers, particularly HPMC with Eudragit RL-100 and PEG, enables slower drug release from diclofenac sodium matrix tablets. This polymer system produced formulations with satisfactory mechanical integrity and desired sustained-release profiles, underscoring the utility of HPMC and PEG in sustained-release formulations

CHAPTER ONE

1.0 INTRODUCTION

Diclofenac sodium is one of the most important nonsteroidal anti-inflammatory drugs (NSAIDs) for managing patients with pain and inflammatory conditions such as arthritis and musculoskeletal disorders (Brogden, R.N. 1980). Its widespread usage underscores its efficacy, yet conventional diclofenac formulations present significant challenges, such as frequent dosing due to a short half-life, and risks of gastrointestinal and cardiovascular side effects that compromise patient safety (Alfaro, R.A. 2023). These clinical issues often contribute to poor adherence, with many patients missing doses or discontinuing therapy, leading to poorly controlled symptoms and increased risk of adverse events (Australian Government Department of Health/ TGA, 2025)

The development of sustained-release tablet technology represents an evolution in pharmaceutical care, aiming to maintain steadier plasma drug concentrations, reduce dosing frequency, and minimize side effects (IRJMETS, 2024). By using advanced blends of hydrophobic and hydrophilic polymers, sustained release formulations of diclofenac sodium provide a therapeutic solution that can improve patient adherence, enhance efficacy, and support safer long-term SAID therapy (Patient.info, 2024).This project investigates the formulation and performance evaluation of sustained-release diclofenac sodium tablets using different polymer combinations, aspiring to enhance pain management and contribute to best practice in pharmaceutical formulation science.

1.1 General Overview of Drug Delivery Systems

Drug delivery systems (DDS) encompass the diverse array of pharmaceutical technologies and formulations designed to administer therapeutic agents in an optimized, controlled, and patient-centric manner (Alam, 2023; Park *et al*., 2021; Taghi *et al*., 2025). Modern pharmacy relies on DDS to enhance drug targeting, improve therapeutic efficacy, and minimize adverse effects, thus supporting improved patient health outcomes and compliance (Alam, 2023; Brown, 2023).

The evolution of DDS has progressed from primitive oral and injectable forms to advanced platforms such as sustained-release tablets, transdermal systems, and nanotechnology-based carriers, reflecting technological and scientific growth over the past century (Taghi *et al*., 2025; Park *et al*., 2021). These advances enable controlled, site-specific delivery, overcoming the limitations of rapid clearance, suboptimal bioavailability, fluctuating plasma levels, and patient inconvenience associated with conventional drug delivery (Alam, 2023; Brown, 2023).

Contemporary DDS integrates biomedical engineering, material science, and pharmacology, yielding smart, responsive drug carriers and personalized therapies. These modern systems are now vital for optimizing therapeutic regimens, facilitating disease management, and supporting the development of advanced therapeutics such as biologics and gene-based medicines (Lopez-Vidal *et al*., 2025; Fiorucci, Urbani, 2024). By overcoming anatomical and physiological barriers, DDS plays a key role in achieving patient-centered outcomes, reducing side effects, and improving overall treatment efficacy (Brown, 2023).

1.1.1 Significance of Sustained Release Formulations in Modern Pharmaceutics

Sustained-release formulations represent a pivotal advancement in pharmaceutical science, offering controlled, prolonged delivery of therapeutic agents that maintain drug concentrations

within the optimal therapeutic window (Patibandla *et al*., 2025; Williams *et al*., 2024). By gradually releasing active ingredients over extended periods, these systems counteract the limitations of immediate-release medications—such as high dosing frequency, fluctuating drug plasma levels, and poor patient adherence (Prakhar *et al*., 2025).

The implementation of sustained release (SR) dosage forms directly enhances therapeutic efficiency and patient compliance by simplifying treatment regimens and reducing missed doses (Williams, 2024; Prakhar, 2018). Uniform drug concentrations produced by SR formulations mitigate adverse effects related to peak-trough fluctuations and lower the risk of toxicity or sub-therapeutic exposure, especially for drugs with short half-lives or narrow therapeutic indices (Rahman *et al*., 2025). Moreover, extended-release platforms are crucial in chronic disease management, allowing personalized therapy and improved quality of life for patients requiring long-term medication (Saini *et al*., 2024).

Recent innovations in SR technology integrate advanced materials, such as hydrophilic polymers and pH-sensitive carriers, facilitating programmable release kinetics that meet diverse therapeutic needs and address pharmaceutical industry demands for cost-effectiveness and regulatory compliance (Jahnavi *et al*., 2025). Collectively, sustained release formulations have revolutionized modern pharmaceutics, balancing efficacy, safety, and patient-centered care (Saini *et al*., 2024).

1.2 Brief Pharmacological Profile of Diclofenac Sodium

Diclofenac sodium is a commonly used nonsteroidal anti-inflammatory drug (NSAID) of the phenylacetic acid class, known for its potent anti-inflammatory, analgesic, and antipyretic properties (Alfaro, 2023). Its primary mechanism of action involves the inhibition of the

cyclooxygenase enzymes (COX-1 and COX-2), which are responsible for the synthesis of prostaglandins and thromboxanes, which are the key mediators of inflammation, pain, and fever (Satar, 2025). Through competitive inhibition of arachidonic acid binding to COX enzymes, diclofenac effectively suppresses the production of prostaglandin E2 (PGE2), leading to reduced pain and swelling in affected tissues (Menasst *et al*., 1978).

Unlike some NSAIDs that selectively target COX-2, diclofenac exhibits a balanced inhibitory effect on both COX-1 and COX-2, with a preference for COX-2 (Alfaro, 2023). This pharmacological profile contributes to its extensive use in the management of acute and chronic musculoskeletal pain, rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and post-operative inflammation (Menasst *et al*., 1978).

The clinical relevance of diclofenac sodium among NSAIDs is a result of its broad therapeutic range and rapid onset of action (Alfaro, 2023). It is often preferred when a strong anti-inflammatory effect is needed, and it remains a reference molecule in comparative studies assessing the efficacy, safety, and tolerability of NSAID therapies for diverse inflammatory conditions (Altman, 2015).

1.2.1 Musculoskeletal Pain

Diclofenac is frequently prescribed for musculoskeletal pain, including osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and gout. In these conditions, it effectively reduces joint pain, swelling, and stiffness, improving mobility and quality of life (Brogden *et al*., 1980).

1.2.2 Back Pain and Soft Tissue Injury

For acute back pain, sprains, strains, and soft tissue injuries, diclofenac is recognized for its rapid onset of action and reliable symptomatic relief. It improves function and supports faster return to activity post-injury (DrugTodayOnline, 2025).

1.2.3 Postoperative and Dental Pain

Diclofenac sodium is widely used for postsurgical pain management, including dental extractions and orthopedic procedures. Its ability to suppress postoperative inflammation makes it valuable for pain control after surgery (Medcentral, 2024).

1.2.4 Migraine and Dysmenorrhea

Diclofenac potassium formulations have approval for use in the acute treatment of migraine and for relief of primary dysmenorrhea (Medcentral, 2024). It provides rapid alleviation of moderate-to-severe pain episodes associated with these disorders.

1.2.5 Chronic Facet Joint Pain and Cancer Pain

Recent studies support diclofenac's role in the management of chronic facet joint pain and as an adjunct in cancer pain therapy, showing significant reductions in breakthrough pain and enhancing patient comfort (Wei *et al*., 2010).

1.2.6 Topical Formulations

The topical forms (gel, solution, patch) of diclofenac have demonstrated benefits in localized musculoskeletal disorders, reducing pain and inflammation in conditions such as tendinitis, bursitis, and minor trauma (Derry *et al*., 2015).

While generally well tolerated, diclofenac shares risks with other NSAIDS in its class, such as potential gastrointestinal, cardiovascular, and renal adverse effects, necessitating careful selection and monitoring in long-term therapy settings (Altman, 2015).

1.3 Problems Associated with Conventional Diclofenac Sodium Formulations

Conventional diclofenac sodium formulations are associated with important pharmacokinetic and safety limitations that restrict their clinical utility and impact patient adherence.

1.3.1 Short Half-life and Frequent Dosing Requirements

Diclofenac sodium is rapidly absorbed and eliminated, with an elimination half-life of 1–2 hours (Leuratti *et al*., 2024; Brogden *et al*., 1980). Consequently, standard oral preparations usually require dosing two or three times per day to maintain adequate plasma concentrations, particularly for chronic pain management. Such frequent dosing can be inconvenient, reducing patient adherence to therapeutic regimens (Leuratti *et al*., 2024).

1.3.2 Gastrointestinal Irritation and Compliance Issues

As a nonselective NSAID, conventional diclofenac sodium formulations can cause damage to gastrointestinal mucosa by inhibiting protective prostaglandin synthesis, resulting in complications like gastritis, peptic ulcers, and gastrointestinal bleeding (Moore *et al*., 2015). These adverse events are more common at higher doses and with prolonged therapy and can lead patients to discontinue treatment or require gastroprotective co-medications (Moore *et al*., 2015).

1.3.3 Adverse Effects Caused by Plasma Level Fluctuations

The immediate-release nature of conventional diclofenac sodium tablets results in marked plasma concentration fluctuations (Brogden *et al*., 1980). Peaks may be associated with

intensified adverse effects (such as upper GI bleeding and elevated cardiovascular risk), while troughs may result in breakthrough pain or subtherapeutic response (Singh *et al*., 2021). Fluctuating exposure significantly increases the risk of both under-treatment and toxicities, restricting the drug's use in long-term pain management (Singh *et al*., 2021).

1.3.4 Adverse Cardiovascular Effects of Diclofenac Sodium

Extensive scientific evidence shows that diclofenac sodium is associated with a heightened risk of major adverse cardiovascular events (MACE) when compared with other NSAIDs and placebo. Recent cohort and population-based studies have shown that diclofenac can precipitate serious events such as myocardial infarction, stroke, heart failure, and cardiac death, regardless of dose or baseline cardiovascular risk (Christiansen *et al*., 2018).

Christiansen *et al*. (2018), in a Danish nationwide cohort study involving hundreds of thousands of patients, found that diclofenac therapy resulted in about a 50% increase in the rate of MACE compared to non-users, including those with and without prior cardiovascular disease. This elevated risk appeared for high doses and was on par with selective COX-2 inhibitors.

Schmidt *et al*. (2023) employed target trial emulation across 300 cohorts and reaffirmed that high doses of diclofenac significantly increased cardiovascular risk, including myocardial infarction, stroke, and cardiac death.

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee, synthesizing meta-analytical data and large observational studies, confirmed that diclofenac use is linked with increased rates of vascular events, primarily coronary events and death from vascular causes (EMA PRAC, 2013).

Diclofenac's adverse cardiovascular profile necessitates careful patient selection and monitoring, particularly in those requiring long-term therapy. Professional guidelines recommend weighing the benefit-risk balance for each patient before initiation.

1.4 Clinical Implications of Frequent Dosing of Diclofenac Sodium

Frequent dosing of conventional diclofenac sodium increases the risk of cumulative and dose-dependent adverse effects across multiple organ systems. This is particularly concerning for patients with chronic pain, where long-term, multiple daily dosing is common.

1.4.1 Gastrointestinal Toxicity

Regular use of diclofenac, particularly at higher or prolonged doses, increases the risk of gastrointestinal ulceration, bleeding, and perforation due to inhibition of protective prostaglandins in the gastric mucosa (Moore *et al*., 2015). The risk is notably correspondent with duration and dose, making frequent dosing especially hazardous for older adults or patients with previous GI pathology (Moore *et al*., 2015).

1.4.2 Renal and Hepatic Impairment

With repeated administration, diclofenac's impact on renal blood flow can cause nephrotoxicity, acute kidney injury, and, rarely, chronic kidney disease (Ahmed *et al*., 2017). High or repeated dosing is also linked to elevations in hepatic transaminases and, in rare cases, significant liver injury (Ahmed *et al*., 2017).

1.4.3 Fluid Retention and Heart Failure

NSAIDs, including diclofenac, can induce fluid retention and exacerbate or precipitate congestive heart failure, risks that are amplified with higher or repeated dosing due to systemic sodium and water retention (Christiansen *et al*., 2018).

1.4.4 Other Systemic Toxicities

Repeated, high-exposure regimens elevate the possibility of dermatological reactions, hematological abnormalities (such as anemia from GI bleeding), and hypersensitivity reactions. Multiple dosing cycles may also increase the risk of cumulative toxicity, even in patients initially tolerant to diclofenac (Ahmed *et al*., 2017).

1.4.5 Neurological Side Effects of Long-Term Diclofenac Sodium Use

Although neurological adverse effects associated with diclofenac sodium are relatively rare compared to its gastrointestinal, renal, and cardiovascular toxicities, several reports and reviews highlight notable central and peripheral nervous system reactions during prolonged or high-dose therapy.

1.4.6 Aseptic Meningitis and Neuropsychiatric Effects

Long-term NSAID usage, including diclofenac, has been linked with cases of drug-induced aseptic meningitis, particularly in patients with autoimmune disorders such as systemic lupus erythematosus (O'Brien *et al*., 1985; Ahmed *et al*., 2017). Presenting symptoms are similar to infectious meningitis and may include headache, fever, photophobia, and nuchal rigidity, but cerebrospinal fluid cultures remain negative. Additionally, isolated neuropsychiatric

manifestations, such as episodes of depression, impaired cognition, and psychosis, have also been reported during extended NSAID treatment courses (Ahmed *et al*., 2017).

1.4.7 Other Neurological Manifestations

NSAID-induced central nervous system effects may include dizziness, vertigo, recurrent falls, drowsiness, encephalopathy, and disorientation, mainly described in case reports of chronic or overdose scenarios (Sulaiman *et al*., 2013). Diclofenac may rarely cause seizures during chronic administration; such effects are typically reversible upon discontinuation (Sulaiman *et al*., 2013).

1.4.8 Mechanistic Insights

Experimental models and mechanistic reviews suggest that diclofenac's neurotoxicity may be related to its capacity to modulate inflammatory mediators (prostaglandins, cytokines), ion channels, and mitochondrial function within neural tissues (Sulaiman *et al*., 2013; ScienceDirect Topics, 2025). Diclofenac has also been observed to impair neuronal stem cell differentiation and survival in vitro, although these findings are preliminary (ScienceDirect Topics, 2025).

These neurological effects are generally infrequent but warrant attention, particularly in long-term, high-dose, or elderly patient populations, and those with underlying neurological or autoimmune conditions.

1.4.9 Compliance Problems

The burden of frequent dosing, side effects, and cumulative risks reduces patient adherence, potentially compromising therapeutic outcomes and increasing the risk of undertreated or poorly controlled pain (Moore *et al*., 2015).

1.5 Clinical Rationale for Sustained-Release Diclofenac Tablets

These adverse profiles highlight the clinical need for sustained-release diclofenac sodium formulations, which provide consistent plasma drug levels, minimize peak-trough fluctuations, reduce dosing frequency, and are designed to limit cumulative tissue toxicity seen with frequent conventional dosing.

The development of sustained-release (SR) formulations of diclofenac sodium is driven by the need to overcome the pharmacokinetic drawbacks and safety concerns related to conventional immediate-release preparations, particularly those amplified by frequent dosing.

1.5.1 Improving Patient Outcomes and Therapy Adherence

SR formulations are engineered to gradually release diclofenac sodium over an extended period, thereby maintaining steady therapeutic plasma concentrations with fewer daily doses (IRJMETS, 2024). This controlled release profile ensures that patients experience consistent symptom control, reducing peaks and troughs that can lead to breakthrough pain or loss of analgesic effect (Moore *et al*., 2015). As a result, patients are more likely to adhere to their medication regimens, with studies showing improved compliance and satisfaction due to lower dosing frequencies and greater convenience (Wisdomlib, 2024; SCIRP, 2023). Enhanced adherence is particularly critical in chronic pain settings, such as osteoarthritis and rheumatoid arthritis, where optimal pain relief and quality of life are dependent on sustained therapy.

1.5.2 Mitigating Side Effects and Optimizing Therapy

Frequent exposure to high plasma peaks of diclofenac, as seen with multiple immediate-release doses per day, raises the risk of gastrointestinal, renal, hepatic, and cardiovascular side effects (Moore *et al*., 2015; Ahmed *et al*., 2017). SR formulations help minimize these risks by

providing a slow, predictable release of the drug, thereby avoiding sharp plasma concentration spikes associated with toxicity (IRJMETS, 2024). Controlled release also reduces direct gastric irritation and decreases the incidence of GI bleeding and ulceration, a significant advantage for patients requiring prolonged NSAID therapy (SCIRP, 2023; Ahmed *et al*., 2017). Moreover, steady-state pharmacokinetics provided by SR tablets may lessen the risk of cumulative organ toxicity and adverse systemic effects.

In summary, by reducing dosing frequency, enhancing adherence, and limiting adverse events, sustained-release diclofenac sodium formulations offer tangible clinical and pharmacological advantages over immediate-release products, helping ensure optimal patient outcomes and safer long-term pain management.

1.5.3 Clinical Evidence Supporting Sustained Release Diclofenac Benefits

Clinical research and comparative trials consistently demonstrate that sustained-release (SR) diclofenac sodium formulations offer significant therapeutic and safety advantages over conventional immediate-release preparations in pain management.

Randomized studies show that SR diclofenac effectively maintains analgesic efficacy in patients with chronic musculoskeletal conditions, including osteoarthritis, rheumatoid arthritis, and soft tissue pain. A 2017 open-label clinical trial found that both SR tablets and transdermal diclofenac patches significantly reduced pain scores over four weeks, with SR diclofenac providing consistent, sustained relief (Shinde *et al*., 2017).

SR diclofenac improves patient compliance by reducing dosing frequency, typically requiring only one or two daily doses rather than three or four for standard tablets. Patients on SR

formulations report higher satisfaction and are more likely to adhere to prescribed regimens, which is critical for long-term control of chronic pain (Varese & Palazzini, 1997).

Evidence also highlights a better gastrointestinal tolerance profile among patients receiving SR diclofenac compared to those on immediate-release tablets. Studies document fewer cases of dyspepsia, gastralgia, and GI pyrosis in patients using prolonged-release formulations, likely due to reduced direct contact with gastric mucosa and more stable plasma levels (Varese & Palazzini, 1997; SCIRP, 2023).

1.5.4 Overview of Sustained-Release Tablets and Their Formulation

Sustained release (SR) tablets represent a major advancement in oral drug delivery, designed to release medication over an extended period at a controlled and predictable rate. The idea behind SR tablets is to maintain consistent therapeutic drug levels, reduce dosing frequency, minimize side effects associated with peak plasma concentrations, and enhance patient compliance, especially in chronic disease management (B Mahato *et al*., 2022; Mohaniya, 2024).

1.5.5 Principles and Mechanisms

SR tablets utilize various mechanisms, primarily:

- **Matrix Systems**: Drug is embedded within a polymeric matrix, and release depends on polymer swelling, diffusion, and erosion. Hydrophilic matrices (e.g., HPMC, xanthan gum) absorb water and swell to form a gel layer, which modulates drug diffusion. Hydrophobic matrices release drugs more slowly, usually by erosion (Mahato *et al*., 2022; Mohaniya, 2024).

- **Coating Systems**: The active pharmaceutical ingredient (API) may be coated with polymers to control the rate of diffusion or dissolution in gastrointestinal fluids (Loknete *et al*., 2025).
- **Osmotic Systems and Ion-exchange Mechanisms**: More sophisticated designs use osmotic pressure or resin polymers to achieve sustained kinetics for specific drugs (Mahato *et al*., 2022).

1.5.6 Formulation Considerations

Designing SR tablets requires:

- Careful selection of polymers and excipients compatible with the drug and desired release profile.
- Safe and stable physical characteristics, ensuring content uniformity, appropriate tablet hardness, and controlled friability (Mahato *et al*., 2022; Mohaniya, 2024).
- Mathematical modeling (e.g., Higuchi, Korsmeyer-Peppas, Hixson-Crowell equations) to predict and optimize drug release rates (Mahato *et al*., 2022).
- Direct compression or wet granulation are common manufacturing techniques; both require uniform drug-polymer mixing to guarantee predictable sustained release (Mahato *et al*., 2022; Mohaniya, 2024).

1.5.7 Clinical and Pharmaceutical Advantages

SR tablets reduce dose frequency, maintain steady plasma concentrations, lower risks of toxicity, and improve patient compliance and therapeutic effectiveness. Especially for drugs with short half-lives or rapid clearance, SR tablets are essential for long-term management and stable drug exposure (Loknete *et al*., 2025; Mahato *et al*., 2022).

1.6 Role of Hydrophobic Polymers in Controlled Drug Release

Hydrophobic polymers play a vital role in the formulation of sustained release (SR) tablets. Their water-insoluble nature forms robust barrier systems that control drug diffusion and prevent rapid drug dissolution, thereby achieving long-term, predictable drug release profiles (Ali *et al*., 2014).

1.6.1 Overview of Key Hydrophobic Polymers

Some commonly used hydrophobic polymers in SR tablet matrix systems include:

- **Ethyl cellulose**: A widely used, non-swellable, water-insoluble polymer that controls drug release primarily via diffusion.
- **Carnauba wax, beeswax, and hydrogenated vegetable oils**: Used as wax matrices, particularly for drugs that are moisture-sensitive or require slower release.
- **Polyvinyl acetate and acrylic polymers (Eudragit RL/RS)**: These synthetic polymers offer tailored permeability and are frequently used in matrix and coating systems (Ali *et al*., 2014; Huang, 1994).

1.6.2 Mechanisms of Drug Release Modulation

In hydrophobic matrix tablets, drug release mostly occurs through one or both of the following mechanisms:

- **Diffusion**: Water penetrates the matrix, dissolving the drug, which then diffuses through the porous polymer network and is gradually released (Huang, 1994).
- **Erosion**: Over time, the outer layers of wax or hydrophobic polymer erode, particularly under the influence of digestive enzymes or mechanical agitation, allowing the embedded drug to be released.

The overall rate and extent of release can be finely tuned by adjusting the polymer content, molecular weight, particle size, and blending with other excipients (Ali *et al*., 2014; Huang, 1994).

1.6.3 Importance of Hydrophobic Polymer-Based SR Tablets

Hydrophobic polymer matrices are especially valuable for drugs with high water solubility, for which hydrophilic matrices might otherwise cause "dose dumping" or too-rapid release. By using hydrophobic polymers, formulators can:

- Achieve sustained, steady-state plasma concentrations.
- Reduce fluctuations in drug levels and lower peak-related side effects.
- Improve the stability of moisture-labile drugs (Ali *et al*., 2014; Huang, 1994).

1.6.4 Eudragit RL-100 in Sustained-Release Tablets

Eudragit RL-100 is a well-established hydrophobic polymer that combines **water-insolubility with controlled permeability**, making it highly effective for creating oral sustained-release dosage forms. It is especially relevant for drugs where slow, predictable release is needed to enhance therapeutic outcomes and minimize dosing frequency.

It is a copolymer of ethyl acrylate, methyl methacrylate, and a low amount of quaternary ammonium groups. It is widely recognized for its functional utility in **sustained and controlled drug delivery**, especially in oral solid dosage forms (Obeidat *et al*., 2009; Evonik, 2025).

1.6.5 Key Properties

- **Hydrophobic Character**: Eudragit RL-100 is hydrophobic, meaning it is water-insoluble, but its structure includes a limited content of quaternary ammonium groups. This imparts controlled permeability to water, which is crucial for tailored, time-controlled drug release (Evonik, 2025).
- **Biocompatibility and Safety**: The polymer is biocompatible and conforms to major pharmacopeia standards (Ph.Eur., USP/NF), making it suitable for pharmaceutical use with minimal toxicity (Evonik, 2025).
- **Versatility**: Supplied as granules, Eudragit RL-100 is used for coating, matrix tablet, microparticle, and nanoparticle systems, and can be blended with other polymers for customized release profiles.

1.6.6 Mechanisms of Drug Release

- **Diffusion-Controlled Release**: The embedded drug diffuses out through the porous matrix formed by Eudragit RL-100. The permeability depends on the amount and distribution of quaternary ammonium groups, which allow limited water penetration and controlled drug diffusion (Obeidat *et al*., 2009; Pignatello *et al*., 2003).
- **Swelling and Erosion**: Under physiological conditions, Eudragit RL-100 may swell slightly due to its semi-permeable nature (higher permeability than Eudragit RS). As the matrix takes up fluid, drug molecules migrate through the hydrated polymer network (Evonik, 2025; Obeidat *et al*., 2009).
- **Influence of Polymer Concentration**: Increasing the content of Eudragit RL-100 in a tablet can slow drug release, provide longer action, and optimize the desired pharmacokinetic profile (Pignatello *et al*., 2003).

1.6.7 Applications in Sustained Release Formulations

- Used in matrix tablets for NSAIDs like diclofenac sodium, Eudragit RL-100 has been shown to produce sustained plasma concentrations, minimize peak/trough fluctuations, and reduce adverse effects associated with frequent dosing (Obeidat *et al*., 2009; Momoh *et al*., 2023).
- It is compatible with various direct compression and solvent evaporation techniques in tablet and bead manufacturing (Obeidat *et al*., 2009).

16.8 Clinical Benefits of Eudragit RL 100 in Sustained-Release Tablets

1. **Consistent Drug Release and Reduced Dosing Frequency**

   Studies have shown that Eudragit RL 100-based SR formulations maintain therapeutic drug concentrations for extended periods, enabling once- or twice-daily dosing instead of conventional multiple daily dosing. This improved pharmacokinetic profile enhances compliance and clinical outcomes for chronic therapies (Obeidat *et al*., 2009; Pignatello *et al*., 2003).

2. **Minimized Peak-Trough Fluctuations**

   Clinical in vitro and in vivo studies confirm that tablets formulated with Eudragit RL 100 provide a steady, gradual release of various drugs, including those with narrow therapeutic indices or short plasma half-lives. Patients benefit from reduced peak-related adverse effects and fewer instances of breakthrough symptoms due to troughs (Pignatello *et al*., 2003; Momoh *et al*., 2023).

3. **Optimized Mechanisms: Diffusion and Erosion**

   Release kinetics of drugs from Eudragit RL 100 matrices typically show an anomalous

(non-Fickian) pattern, combining diffusion through the hydrated polymer with polymer erosion. This mechanism can be fine-tuned by adjusting polymer concentration, tablet size, and processing method, offering formulators precise control over drug delivery rates (Pignatello *et al*., 2003; Indian J Pharm Sci, 2021).

4. **Enhanced Bioavailability of Poorly Soluble Drugs**

   When used in matrix tablets or microspheres, Eudragit RL 100 can enhance dissolution and oral bioavailability of otherwise insoluble drugs. For instance, a recent study with fluvastatin sodium found that Eudragit RL 100-based SR tablets not only sustained drug release up to 24 hours but also improved overall drug dissolution (Indian J Pharm Sci, 2021).

5. **Improved Gastrointestinal Tolerance**

   Clinical and preclinical assessments suggest that steady-release profiles reduce the risk of gastrointestinal irritation related to high concentrations of NSAIDs like diclofenac or other irritant drugs, a major advantage for patient safety and long-term use (Pignatello *et al*., 2003).

1.7 Role of Hydrophilic Polymers in Controlled Drug Release

Hydrophilic polymers are commonly used in the design of controlled and sustained release oral dosage forms, especially matrix tablets. Their unique ability to rapidly hydrate, swell, and form viscous gels upon contact with gastrointestinal (GI) fluids enables them to maintain drug release over prolonged periods (Nokhodchi *et al*., 2012).

1.7.1 Common Hydrophilic Polymers

- **Hydroxypropyl methylcellulose (HPMC)**: It is the most widely used hydrophilic matrix polymer for both synthetic and natural drug carriers. It rapidly forms a gel layer, controls water entry, and enables reproducible release. It is non-toxic and compatible with a wide array of drugs (Alderman, 1984; Nokhodchi *et al*., 2012).
- **Xanthan gum, sodium alginate, carrageenan, carbopol, and polyethylene oxide**: These polymers differ in viscosity, water affinity, and gelling properties, but they all create diffusion barriers critical for extended release (Nokhodchi *et al*., 2012; IRJMETS, 2024).

1.7.2 Mechanisms of Drug Release

- **Hydration, Swelling, and Gel Layer Formation**: Upon exposure to water, hydrophilic polymers hydrate and swell, creating a gelatinous barrier surrounding the tablet. The thickness and viscosity of this layer are crucial for determining the rate of drug release (Nokhodchi *et al*., 2012; Alderman, 1984).
- **Diffusion**: For water-soluble drugs, release from the hydrophilic matrix is often controlled by diffusion through the hydrated gel barrier. The process follows Fick's law, with the gel thickness, polymer grade, and drug properties determining the release rate (Nokhodchi *et al*., 2012; Johnson *et al*., 1993).
- **Erosion**: For less soluble or high-dose drugs, polymer erosion also becomes a major contributor. As the gel layer gradually erodes (disintegrates), the drug embedded within is released (Nokhodchi *et al*., 2012; Skoug *et al*., 1993).

- The final release profile is typically a combination of diffusion and matrix erosion (non-Fickian or anomalous transport), often modeled mathematically to ensure predictable in vivo behavior (Nokhodchi *et al*., 2012; Sujja-areevath *et al*., 1998).

1.7.3 Importance of Hydrophilic Polymer Blends

The use of polymer blends (e.g., HPMC with xanthan gum) offers superior control and customization of release kinetics. Such combinations allow for fine-tuning matrix porosity, swelling/erosion rates, and mechanical strength, providing greater formulation flexibility for drugs with varying physicochemical properties (Nokhodchi *et al*., 2012; IRJMETS, 2024).

1.7.4 Clinical impact

Hydrophilic polymer-based SR tablets exhibit consistent, pH-independent release; prolong plasma drug levels; and reduce gastrointestinal irritation and patient adherence issues seen with conventional dosing (Nokhodchi *et al*., 2012; DNV *et al*., 2022). Formulations utilizing HPMC as a matrix have demonstrated increased oral absorption and improved clinical efficacy relative to immediate-release forms (DNV *et al*., 2022).

1.7.5 Hydroxypropyl Methylcellulose (HPMC) in Controlled Drug Release

HPMC is a semi-synthetic, non-ionic cellulose ether known for its high biocompatibility, safety, and versatility in pharmaceutical formulations. It is available in multiple viscosity grades (e.g., K4M, K15M, K100M), and it is highly valued for forming robust, pH-independent gels when hydrated, making it a core material in oral sustained and controlled release matrix systems (Mašková *et al*., 2020; Vlad *et al*., 2025).

1.7.6 Mechanism of Action in Sustained-Release Tablets

- **Gel Layer Formation:** Upon exposure to gastrointestinal fluids, HPMC rapidly hydrates and swells to form a viscous gel layer around the tablet. This gel serves as both a physical barrier to drug diffusion and a modulator of water ingress (Nokhodchi *et al*., 2012; Vlad *et al*., 2025).
- **Drug Release by Diffusion and Erosion:** For water-soluble drugs, drug molecules diffuse through the hydrated gel at a controlled rate, while for poorly soluble substances, drug release is predominantly a function of polymer erosion. Both processes are tunable by adjusting HPMC type and concentration (Alderman, 1984; Sekharan *et al*., 2011).
- **Sustained, Predictable Profiles:** The thickness, strength, and viscosity of the HPMC gel directly control the rate of drug release, permitting extended release lasting 8–24 hours from a single dose (Nokhodchi *et al*., 2012; Sekharan *et al*., 2011).

1.7.7 Clinical Benefits

- **Improved Patient Compliance:** HPMC-based matrices allow for convenient once- or twice-daily dosing, enhancing adherence for chronic conditions (Mašková *et al*., 2020; Vlad *et al*., 2025).
- **Flexibility and Compatibility:** HPMC is suitable for a vast range of actives, such as acidic, basic, or neutral, and is unaffected by GI pH variations, supporting broad applications (Vlad *et al*., 2025).
- **Favorable Safety Profile:** It is inert, non-toxic, and does not trigger irritation or allergic reactions, making it ideal for long-term therapy (Mašková *et al*., 2020; Vlad *et al*., 2025).

1.7.8 Formulation Versatility

- HPMC can be used alone or in combination with other hydrophilic or hydrophobic polymers, enabling formulators to customize release kinetics further (Naseera *et al*., 2025).
- Its binding, gelling, and thickening properties also make it useful for granulation, coating, and film formation in modified-release systems (Mašková *et al*., 2020; Vlad *et al*., 2025).

1.7.9 Polyethylene Glycol (PEG) in Controlled Drug Release

Polyethylene glycol (PEG) is a versatile, non-toxic, and highly water-soluble polymer used widely in sustained release and controlled drug delivery systems. PEG's hydrophilic nature enables it to rapidly absorb water, swell, and create diffusion pathways in tablet matrices, which significantly impacts drug solubility and release profiles (Padín-González, 2022).

1.7.10Mechanism of Controlled Release

- In matrix tablets, PEG functions both as a pore-former and dissolution enhancer. Once hydrated, PEG swells and creates a hydrophilic environment, facilitating the release of drugs, especially those with poor water solubility (Nascimento *et al*., 2020).
- The amount and molecular weight of PEG used determine the rate of drug diffusion and the ultimate release profile. Typically, higher PEG content yields faster release due to greater matrix porosity, while lower PEG concentrations (or combination with other gelling agents like HPMC) slow the release for extended action (Nascimento *et al*., 2020; Mesnukul *et al*., 2009).

1.7.11 Benefits of PEG in Sustained Release Systems

- **Enhanced Drug Dissolution:** PEG acts to increase the solubility and dissolution rate of drugs by providing a hydrophilic microenvironment. This is especially advantageous for poorly soluble drugs and solid dispersion systems (Mesnukul *et al*., 2009).
- **Customizable Release Profiles:** By combining PEG with other polymers (e.g., HPMC), formulators can fine-tune the desired release rate—balancing the need for initial burst release with long-term sustained action (Mesnukul *et al*., 2009).
- **Low Toxicity and Excellent Safety:** PEG is highly biocompatible and is used as a carrier in numerous marketed pharmaceuticals, including sustained, delayed, and targeted release drugs (Padín-González, 2022).

1.7.12 Maize Starch Mucilage as a Hydrophilic Polymer in Controlled Drug Release

Maize starch mucilage is a plant-derived, polysaccharide-rich biopolymer commonly utilized as an excipient in pharmaceutical formulations, notably as a **hydrophilic agent**. Its structure is comprised primarily of amylose and amylopectin, which grants a high affinity for water, enabling it to swell, gel, and act as an effective matrix former for controlled and sustained release tablets (Kurniawansyah *et al*., 2022).

1.7.13 Functional Roles and Mechanisms

- **Swelling and Gelation:** Upon exposure to gastrointestinal fluids, maize starch mucilage rapidly hydrates, swells, and forms a viscous gel layer around the tablet. This hydrated matrix impedes immediate drug dissolution, allowing for regulated release over time (Kurniawansyah *et al*., 2022).

- **Diffusion Control:** The hydrated mucilage matrix serves as a diffusion barrier, slowing the migration of drug molecules from the tablet core into surrounding fluids. The rate of release can be modulated by the quantity and physical properties of the maize starch mucilage used (Tosif *et al*., 2021).
- **Biocompatibility and Safety:** Maize starch and its mucilage are biocompatible, non-toxic, biodegradable, and inexpensive, making them attractive for pharmaceutical use and particularly suitable for patient-friendly, natural matrix systems (Kurniawansyah *et al*., 2022; Tosif *et al*., 2021).

1.7.15 Clinical and Pharmaceutical Applications

- Widely used as a binder, disintegrant, and matrix agent, maize starch mucilage is compatible with other hydrophilic polymers such as HPMC and PEG. In sustained release formulations, it has been shown to prolong drug release and reduce burst release phenomena, especially for highly soluble actives (Kurniawansyah *et al*., 2022).
- Beyond controlled-release matrices, maize starch mucilage improves tablet compressibility, mechanical strength, and friability, which are essential parameters in robust tablet manufacturing (Kurniawansyah *et al*., 2022).

1.8 Formulation of Sustained-Release Tablets Using Hydrophobic and Hydrophilic Polymer Blends

The combination of hydrophobic and hydrophilic polymers in matrix tablet formulations offers a versatile strategy to precisely control drug release profiles, optimize therapeutic efficacy, and enhance formulation robustness. This synergistic approach leverages the unique advantages of

each polymer class to maximize release modulation and minimize dose dumping or burst effects (Wadher *et al*., 2011).

Wadher *et al*. (2011) demonstrated that the combination of synthetic hydrophobic (e.g., Eudragit) and natural hydrophilic polymers (e.g., maize starch or HPMC) yields sustained release matrices with superior release control compared to systems using single polymer types. A 2024 study (Olsson *et al*., 2024) found that increasing hydrophobic content narrows the hydrophilic domains within tablet matrices, slowing overall drug diffusion and enabling precise temporal release modulation.

1.8.1 Advantages of Blending Hydrophobic and Hydrophilic Polymers

- **Hydrophilic Polymers** (e.g., HPMC, maize starch mucilage, PEG) rapidly hydrate, swell, and form gel layers upon contact with GI fluids, allowing controlled drug diffusion through the hydrated matrix. These gel systems are particularly effective at retarding the release of water-soluble drugs and can significantly reduce inter- and intra-subject absorption variability.
- **Hydrophobic Polymers** (e.g., Eudragit RL-100, carnauba wax, ethyl cellulose) resist water penetration, creating a more rigid and less permeable matrix. They are especially effective for sustaining the release of highly soluble drugs and for improving tablet stability in moisture-rich environments (Mahato *et al*., 2022).

When blended, these polymers benefit from **complementary mechanisms**:

- The hydrophilic agent swells and forms channels for initial diffusion, while the hydrophobic agent slows water ingress and further diffusion, leading to a more uniform, prolonged release.
- Blends can achieve **zero-order or non-Fickian (anomalous) release kinetics**, which are ideal for chronic therapies requiring steady-state plasma levels (Wadher *et al*., 2011; Mahato *et al*., 2022).
- Polymer ratio adjustment enables formulators to tailor release rates for specific drugs and target indications—blending allows flexible modulation unattainable by single polymers alone (Olsson *et al*., 2024).

1.8.2 Pharmaceutical and Clinical Benefits

- **Reduced Dosing Frequency**: Enables once- or twice-daily dosing, improving compliance in chronic therapy.
- **Minimized Initial Burst Release**: The hydrophobic matrix component prevents excess immediate drug release.
- **Improved Tablet Physicochemical Properties**: Enhanced compressibility and mechanical strength, particularly with natural starches or HPMC for binding.
- **Stable, Reliable Release**: Blends are less susceptible to environmental agitation, food effects, or minor manufacturing variations.

1.8.3 Challenges in Formulating Sustained-Release Diclofenac Sodium Tablets

Formulating sustained-release (SR) diclofenac sodium tablets is a complex process that involves overcoming significant technical and clinical obstacles to achieve reproducible, safe, and therapeutically effective products.

1.8.4 Technical Challenges

- **Selection and Compatibility of Polymers:** Achieving reliable sustained release depends on optimizing the ratio and interaction of hydrophobic (e.g., Eudragit RL-100) and hydrophilic (e.g., HPMC, maize starch mucilage, PEG) polymers. Variations in polymer properties, batch-to-batch consistency, and drug-polymer interactions can influence release kinetics, stability, and manufacturability (Wadher *et al*., 2011).
- **Drug-Polymer Interaction:** Diclofenac sodium's slight solubility and poor flow properties require careful selection and blending of polymers to achieve desired dissolution and uniformity (JAPSONLINE, 2025). Failure to optimize these interactions can lead to incomplete release, dose dumping, or unanticipated variability in drug absorption.
- **Compression and Process Parameters:** Tablet hardness, granulation technique (wet vs. direct compression), and compaction force affect matrix integrity and drug release. Over-compression may impede water access and limit release rates, while insufficient compression compromises tablet robustness (Amdework *et al*., 2025).

1.8.5 Clinical Challenges

- **Interpatient and Intrapatient Variability:** Differences in gastric pH, motility, and enzyme activity affect matrix hydration and erosion, resulting in unpredictable in vivo release and absorption (Drapińska *et al*., 2025).
- **Incomplete Control of Adverse Effects:** While SR formulations can reduce GI irritation and improve tolerability by lowering peak plasma concentrations, they do not eliminate the underlying risks associated with long-term NSAID use, especially for at-risk patients (Drapińska *et al*., 2025).

1.8.6 Need for Optimized Polymer Interaction

- Blending hydrophilic and hydrophobic polymers allows more fine-tuned, robust release mechanisms. Experimental studies demonstrate that optimized blends can achieve zero-order kinetics and match reference SR products in dissolution performance (Wadher *et al*., 2011; JAPSONLINE, 2025).
- Advanced modeling and formulation design, including the use of natural and synthetic polymers together, is required to minimize batch variability and maximize clinical predictability (Amdework *et al*., 2025).

1.8.7 Industrial and Therapeutic Implications

- **Manufacturing:** Scale-up from lab to industry can introduce physical and chemical challenges, requiring careful validation of tablet uniformity, stability, and reproducibility under varied environmental and process conditions (JAPSONLINE, 2025).
- **Patient-Centered Therapy:** High-quality SR diclofenac sodium tablets have the potential to improve compliance, reduce dosing frequency, and lower side effect profiles. However, clinical translation depends on robust in vitro–in vivo correlation and continued monitoring of safety/tolerability in long-term therapy (Drapińska *et al*., 2025).

1.9 Justification of the Study

This study contributes to pharmaceutical science by providing insight into the design and development of sustained release formulations utilizing rational polymer blends. By investigating how hydrophobic and hydrophilic polymer interactions can be leveraged for controlled and extended drug delivery, this research addresses current challenges in NSAID therapy—minimizing side effects, reducing dosing frequency, and improving therapeutic

outcomes. The findings will support industrial innovation in tablet formulation, encourage best practices for excipient selection, and foster safer, more

2.0 Aim and Objectives of the Study

AIM

i. To formulate and evaluate sustained-release Diclofenac sodium matrix tablets using Eudragit RL-100 in combination with different hydrophilic polymers (HPMC and maize starch mucilage with PEG), in order to compare their effects on tablet properties and drug-release behaviour and to determine which hydrophilic polymer system is more suitable for sustained release.

OBJECTIVES

i. To prepare sustained-release diclofenac sodium tablets incorporating various blends of hydrophilic polymers.
ii. To assess the physicochemical properties and quality attributes (hardness, friability, disintegration, dissolution profile) of the different tablet formulations.
iii. To systematically evaluate and compare drug release profiles to determine which polymer blend yields the most desirable sustained release effect.

CHAPTER TWO

2.0 MATERIALS AND METHODS

2.1 MATERIALS/EQUIPMENT

i. Diclofenac sodium (active ingredient)
ii. Eudragit RL-100 (hydrophobic polymer)
iii. Maize starch mucilage (hydrophilic polymer)
iv. Ethanol (solvent)
v. Propylene glycol (PEG) (plasticizer)
vi. Hydroxypropyl methylcellulose (HPMC) (binder or release modifier)
vii. Lactose (filler/diluent)
viii. Magnesium stearate (lubricant)
ix. Talc (TAC) (glidant)

2.2 METHOD

2.2.1 Preparation of Sustained-Release Diclofenac Tablets

The sustained-release diclofenac sodium tablets were prepared using the coacervation method. 50 mL of ethanol was measured into a beaker, and the required quantity of Eudragit RL-100 was added. The mixture was placed in a magnetic stirrer and stirred until the Eudragit completely dissolved. After complete dissolution, the weighed quantity of diclofenac sodium was added to the solution and stirred continuously until it also dissolved.

Once a uniform solution was obtained, it was removed from the magnetic stirrer, covered with aluminum foil to prevent ethanol evaporation, and left to stand overnight for sorption.

The following day, the other formulation components, lactose, polyethylene glycol (PEG), talc, and magnesium stearate were added in their respective quantities. The mixture was again placed on the magnetic stirrer and stirred for about 5–10 minutes to ensure uniform mixing. The resulting mixture was then poured into a stainless steel tray and dried in an oven. After drying, the mass was removed, transferred into a beaker, and then pulverized using a mortar and pestle to obtain a fine powder. The powder was subsequently passed through a 425 µm sieve to ensure uniform particle size.

The resulting granules were subjected to pre-compression evaluations such as flow rate, angle of repose, bulk density, and tapped density. After these tests, the desired quantity of granules was weighed and compressed into tablets using a tablet press.

2.3 EVALUATION OF PHYSIOCHEMICAL PROPERTIES OF SUSTAINED-RELEASE DICLOFENAC TABLETS

2.3.1 Determination of Bulk Density

A weighed amount of the sustained-release diclofenac powder was poured into a 50ml glass measuring cylinder, and the bulk volume was determined. The bulk density (Dь) was calculated by dividing the weight (m) by the volume (V_0).

$D_ь = m/V_0$……..1

2.3.2 Tapped Density

The Tapped Density was determined by tapping the measuring cylinder containing the weighed sustained-release diclofenac powder 100 times and the volume obtained was recorded. The

tapped volume (D_t) was determined by dividing the mass (m) by the volume (V_{100}) obtained after tapping.

$D_t = m/V_{100}$……2

2.3.3 Flow Rate

This is the mass of a substance which passes through a given orifice per unit time (kg/s). A weighed amount of the sustained-release diclofenac powder was allowed to flow under gravity through an orifice with a diameter of 0.85cm, and the time taken to flow through the orifice was recorded. Flow rate was computed using the formula:

Flow rate = Mass (kg)/time (sec)…….3

2.3.4 Angle of Repose

The Angle of repose is the steepest angle of descent or dip of the slop relative to the horizontal plane when the material on the slope face is on the verge of sliding. A weighed amount of the sustained-release diclofenac powder was poured through a funnel until the apex of a cone was formed. The diameter at the base of the cone and the maximum height of the cone were measured and used to calculate the angle of repose. The Angle of Repose was calculated from the equation below:

$\tan \theta = 2h/d$……..4

Where;

θ = angle of repose

h = height of cone

D = diameter of base of cone

2.3.5 EVALUATION of Carr's index and Hausner ratio

$CI = (D_t - D_b / D_t) \times 100$……..5

$HR = D_t / D_b$…….6

Where

CI = Carr's Index (expressed in %)

HR = Hausner's ratio

D_t = Tapped density

D_b = Bulk density

Carr's Index and Hausner's ratio are used to determine the flowability of the powders. Lower Hausner's ratio values (<1.25) indicate better flow properties than higher values (>1.25).

2.4 PREPARATION OF TABLETS

A total of ten batches (E1-E10) of tablets were formulated, with each batch having not less than 40 tablets. The first five batches (E1-E5) were formulated with HPMC, while the remaining five batches of tablets (E6-E10), were formulated with maize starch mucilage. The tablets were prepared via direct compression using the formula in Table 1.0. Tableting was done with a single-punch tableting machine (Manesty machines, UK). The target of Diclofenac sustained-release tablets was 300mg at a compaction pressure of 40kN.

The resulting tablets were characterized for dimensions, weight uniformity, hardness, friability, disintegration time, and dissolution time.

Table 1.0 Formula for preparation of Diclofenac sustained-release tablets (with HPMC)

Ingredient in (mg)	**Quantity (mg)**				
	batches				
	E1	E2	E3	E4	E5
Diclofenac NA	75	75	75	75	75
Eudragit rl100	20	20	20	20	20
HPMC	45	45	45	45	45
PEG	20	25	30	35	40
Lactose	128	123	118	113	108
Magnesium sterate	6	6	6	6	6
Talc	6	6	6	6	6
Total weight	300	300	300	300	300

Table 1.2 Formula for preparation of Diclofenac sustained-release tablets (with maize starch mucilage)

Ingredient in (mg)	**Quantity (mg)** **batches**				
	E6	E7	E8	E9	E10
Diclofenac NA	75	75	75	75	75
Eudragit rl100	20	20	20	20	20
Maize starch mucilage (15% w/v)	45	45	45	45	45
PEG	20	25	30	35	40
Lactose	128	123	118	113	108
Magnesium sterate	6	6	6	6	6
Talc	6	6	6	6	6
Total weight	300	300	300	300	300

2.5 CHARACTERIZATION OF TABLETS

2.5.1 Weight Uniformity

The weight of at least 20 tablets from each of the ten batches was measured with an electronic weighing balance (MT-200, Metklar, Switzerland), and the average weight of the tablets was calculated.

2.5.2 CRUSHING STRENGTH

Hardness is defined as the crushing strength of a tablet of the force required to break the tablet diametrically, which determines the ease of handling and rigors of transportation. For each batch, 10 tablets were used for the hardness test. The hardness of each tablet was determined using a Monsanto tester.

2.5.3 Friability of Tablets

The friability of tablets is a value that predicts the likelihood of a tablet breaking into smaller pieces in transit and use. A total of 10 tablets per batch were pre-weighed and then placed in the drum of a friabilator (Erweka Apparatebau, Germany). The apparatus was operated at 25 revolutions per minute (25rpm) for 4 minutes. Afterward, the tablets were dusted and reweighed. The friability was calculated using the formula:

$$\text{Friability} = (W_i\text{-}Wf/W_i) \text{ X } (100/1) \quad \text{.....7}$$

Where

W_i = Initial Weight of tablets before test

Wf = Final Weight of tablets after test.

2.3.4 Tablet Disintegration Test

The disintegration times of the tablets were determined in distilled water at 37°± 0.5℃ using a B.P. disintegration test unit (MK IV, Manessty machines, UK). One tablet was introduced into each of the six tubes. This was then suspended in a beaker containing distilled water and was oscillated by the device until all the fragments of the disintegrated tablets passed through the mesh of the basket. The disintegration times were recorded and the mean calculated.

2.5.5 Dissolution profile of Diclofenac sustained-release Tablets

Dissolution test for the tablets was carried out using the USP2 paddle apparatus. A 900ml volume of 0.1N HCL was introduced into three vessels of the three-chambered dissolution apparatus, and the dissolution medium temperature was maintained at 37.0 ± 0.5℃. One tablet was placed in the basket of each of the three vessels containing 0.1N HCL. The apparatus was switched on and operated at 100rpm for the first two hours, and switched to 900ml phosphate buffer solution (pH 7.4) for 6h. A 5ml volume of dissolution fluid was withdrawn at pre-determined intervals, and the withdrawn volume was replenished with the same volume of fluid with the same temperature and pH as the dissolution fluid. The absorbance of the resulting solution was read at 274nm using 0.1N HCL as a blank. Triplicate analyses were performed, and the mean values, accompanied by their corresponding standard deviations, were documented.

CHAPTER THREE

3.0 RESULTS AND DISCUSSION

3.1 EVALUATION OF PHYSICOCHEMICAL PROPERTIES OF DICLOFENAC SOIDUM (POWDER)

The powdered blends were evaluated for bulk density, tapped density, angle of repose, Hausner's ratio, and Carr's index, and the results are shown in Table 3.1.

Table 3.1 Properties of Diclofenac Sodium sustained-release tablets

Batch	Bulk Density(g/cm^3)	Tapped Density(g/cm^3)	Carr's Index(%)	Hausner's Ratio	Angle of repose (^{o})
E1	0.57	0.63	8.00	0.91	18.81
E2	0.53	0.66	19.69	0.80	18.74
E3	0.5	0.54	7.40	0.92	22.79
E4	0.45	0.50	10	0.90	29.16
E5	0.41	0.47	12.76	0.87	26.73
E6	0.59	0.65	9.23	0.91	28.89
E7	0.57	0.63	9.52	0.90	34.11
E8	0.55	0.62	11.29	0.88	19.04
E9	0.55	0.61	9.84	0.90	25.43
E10	0.52	0.59	10.86	0.89	24.86

3.1.2 Bulk Density

Bulk density reflects how efficiently powder particles consolidate in their loose, unpacked state. This provides insight into potential tablet weight consistency and uniformity during compression. During this study, the observed bulk density values for the powder blends spanned from 0.41 to 0.59 g/cm³. As specified by USP guidelines, powders exhibiting bulk densities between 0.25 and 0.65 g/cm³ are regarded as having satisfactory packing and flow attributes suitable for tablet manufacturing. The results attained here are within the optimal range, indicating that every formulation demonstrated good bulk packing characteristics, making them appropriate for direct compression techniques.

Notably, batch E9 displayed a relatively higher bulk density (0.55 g/cm³), suggesting a more compact arrangement of particles that may support uniform tablet weights during compression. In contrast, batch E5, with a lower bulk density of 0.41 g/cm³, may be indicative of a more open or porous blend.

3.1.3 Tapped Density

Tapped density demonstrates the behavior of a powder under applied compression. It is measured by pouring the powder into a measuring cylinder and repeatedly tapping the cylinder until the volume stabilizes. In this study, tapped density readings for the powder blends spanned 0.47 to 0.66 g/cm³, which fits well within the standard USP range for powders and granules (0.40 to 0.80 g/cm³). These results demonstrate that the samples exhibited adequate compressibility and could be compacted into tablets without significant concerns such as capping or lamination. The notably higher tapped density found in batch E2 (0.66 g/cm³) indicates efficient particle

rearrangement and packing when subjected to tapping, a feature that is likely to enhance tablet mechanical strength.

3.1.4 Carr's Index

Carr's Index is a recognized indicator of powder compressibility, derived from the comparison between bulk and tapped density measurements. The USP classification states that values below 15% denote excellent flow characteristics; 15–20% suggest good flow; 20–35% are considered fair to passable; and values greater than 35% reflect poor flow properties. In this investigation, Carr's Index values were observed to range from 7.40% to 19.69%, suggesting that most of the batches had excellent to good flowability. Specifically, all batches except batch E2 registered values under 15%, representing very good compressibility and flow for direct tablet compression.. Nonetheless, all batches remained within acceptable parameters for tablet manufacture, as no issues with segregation or capping arose during compression. This outcome reinforces that all batches exhibited suitable flow and compaction qualities for consistent tablet production.

3.1.5 Hausner's Ratio

Hausner's ratio is a key parameter for evaluating powder flow. It is calculated as the ratio of tapped density to bulk density. The USP designates this metric as a standard assessment of flowability, with values below 1.25 indicating good flowability, values from 1.25 to 1.5 reflecting passable flow, and those greater than 1.5 pointing to poor flow. In this study, Hausner's ratio values for the 10 batches spanned from 0.80 to 0.92, signifying that all of the formulations demonstrated good flow characteristics. Batch E2 displayed the lowest ratio of 0.80, indicative of superior flow properties. All measured values fell within the USP-

recommended range, supporting the suitability of all 10 batches for direct compression, without the need for additional flow aids.

3.1.4 Angle of Repose

The angle of repose sis a direct measure of powder flowability and is determined by the steepness of the cone formed when the powder is allowed to flow through a funnel. According to USP specifications, values below 30° denote excellent flow, 30–40° indicate good flow, 40–45° represent passable flow, while angles above 45° reflect poor flow characteristics.

In this study, the angles of repose ranged from 18.74° to 34.11°, signifying that the powder blends exhibited good to passable flow properties. Among the formulations, E2 (18.74°) demonstrated the best flow, whereas E7 (34.11°) showed the least. The favorable flow of all formulations facilitated smooth die filling during tablet compression, resulting in uniform tablet weight and thickness.

Table 3.3 Flow properties of powders in relation to Angle of repose values

Flow property	Angle of repose(°)
Best flow	<25
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very, very poor	>66

3.3 CHARACTERIZATION OF TABLETS

The following results were obtained from the tests carried out on the tablets in Batches E1-E10.

Table 3.5 Characterization of Diclofenac Sodium Sustained-Release Tablets

Batch	Tablet Weight(mg)	Tablet Crushing Strength(KP)	Friability(%)	Disintegration Time(Mins)
E1	291.05 ± 2.15	6.75 ± 0.14	0.05	394.33 ± 25.33
E2	298.25 ± 0.66	6.88 ± 0.13	0.19	357.33 ± 27.35
E3	292.90 ± 3.01	6.75 ± 0.14	0.14	355.67 ± 33.13
E4	296.5 ± 2.74	6.5 ± 0.14	0.03	384.17 ± 20.14
E5	291.20± 4.50	3.88 ± 0.72	0.07	315.50 ± 30.10
E6	293.25 ± 1.19	5.03 ± 0.21	0.14	65.17 ± 2.14
E7	285.30 ± 1.58	3.38 ± 0.24	0.14	64.51 ± 1.87
E8	295.85 ± 1.42	4.00 ± 0.35	0.20	45.24 ± 0.32
E9	292.55 ± 2.28	3.50 ± 0.30	0.20	35.54 ± 3.36
E10	292.98 ± 2.17	3.20 ± 0.25	0.19	25.6 ± 2.0

3.3.1 Weight Uniformity

Weight uniformity is a compendial quality control test specified in major pharmacopoeias, including the British Pharmacopoeia (BP) and the United States Pharmacopeia (USP), to ensure consistent dosage across tablets of the same batch. Variations in individual tablet weights are often attributed to non-uniform flow of granules or powder during die filling, which can result in uneven compression. According to the BP specification, not more than two of the individual weights of twenty tablets may deviate from the average weight by more than ± 5%, and none should deviate by more than twice this limit.

In this study, the formulated Diclofenac sodium sustained-release tablets had mean weights ranging from 285.30 ± 1.58 mg to 298.25 ± 0.66 mg, all of which fell within the acceptable pharmacopoeial range of 285 mg to 315 mg (± 5%). This indicates satisfactory weight uniformity across all ten batches. This is important because maintaining uniform tablet weight is essential for ensuring accurate dosing and consistent therapeutic performance.

Table 3.6 Pharmacopoeia weight limits of uncoated tablets.

Pharmacopoeia	**Tablet weight range (mg)**	**Not more than two differ from mean by more than ± (%)**	**None differ form mean by more than ± (%)**
British Pharmacopoeia	≤80	10	15.0
	80-250	7.5	12.5
	≥250	5.0	10.0
United States Pharmacopoeia	≤130	10	20.0
	130-324	2.5	15.0
	≥324	5.0	10.0

3.3.2 TABLET HARDNESS/ CRUSHING STRENGTH DETERMINATION

Tablet hardness (or crushing strength) is a key physical quality parameter that indicates a tablet's ability to withstand mechanical stress during handling, packaging, and transportation. It is influenced by formulation variables such as polymer binder type, compression force, particle size distribution, and excipient interactions. While the USP does not specify a fixed numerical hardness value, it recommends that tablets possess sufficient mechanical integrity to resist chipping or breakage while still allowing for appropriate performance.

In this study of sustained-release Diclofenac sodium tablets, hardness values ranged from 6.88 ± 0.13 kg/cm^2 (Batch 2) down to 3.20 ± 0.25 kg/cm^2 (Batch 10). The first five batches (formulated with Eudragit RL-100 + PEG + HPMC) exhibited relatively higher hardness (3.88–6.88 kg/cm^2), which can be attributed to the gel-forming and binding characteristics of HPMC combined with the hydrophobic Eudragit matrix. By contrast, batches 6-10 (which replaced HPMC with maize starch mucilage) displayed reduced hardness (3.20–5.03 kg/cm^2). This reduction is likely due to the more hydrophilic and less cohesive nature of maize starch mucilage, which, although it aids disintegration and wettability, provides less mechanical reinforcement than HPMC. The downward trend in hardness aligns with the change in hydrophilic polymer design: as maize starch mucilage content increased, tablet matrices became less rigid and easier to disintegrate.

Overall, all formulations maintained adequate mechanical integrity for handling and packaging despite the formulation changes. The data suggest that while maize starch mucilage may lower tablet hardness compared to HPMC, it still supports acceptable hardness in combination with Eudragit RL-100 and PEG.

3.3.3 FRIABILITY OF TABLETS

Friability is a key quality control test that assesses a tablet's ability to resist mechanical abrasion and chipping during handling, packaging, and transport. The test typically involves rotating a known number of tablets in a friabilator and measuring the percentage weight loss, which reflects the robustness of the tablet and the strength of inter-particle bonds formed during compression. According to USP, the allowable limit for friability of compressed tablets is typically ≤ 1 % weight loss; values beyond this may indicate inadequate mechanical integrity or poor binder efficiency.

In this investigation of sustained-release diclofenac sodium tablets, friability ranged from 0.03 % to 0.20 % across 10 formulation batches. All values fall well below the USP threshold of 1 %, indicating excellent mechanical resistance of the tablets under the applied conditions. In the first five batches (Eudragit + PEG + HPMC), the low friability reflects the cohesive matrix formed by HPMC swelling and the hydrophobic barrier from Eudragit, which reduces surface damage during tumbling. For batches 6–10 (Eudragit + PEG + maize starch mucilage), the continued low friability demonstrates that despite replacing HPMC with maize starch mucilage, the tablets retained sufficient compactness and abrasion resistance. Past experimentation has shown that while unmodified starches may lead to higher friability when used in high concentrations, when used appropriately as mucilage binders, the friability can remain within acceptable limits.

Overall, the consistently low friability values across all batches confirm that the chosen compression conditions, binder-polymer combinations, and excipient ratios achieved tablets with adequate mechanical integrity suitable for manufacturing, packaging, and distribution even with the swap from HPMC to maize starch mucilage.

3.3.4 TABLET DISINTEGRATION TIME

Disintegration testing assesses the time required for a tablet to break down into smaller granules or particles when exposed to aqueous media under standardized conditions. For sustained-release formulations, disintegration time reflects the polymer matrix's integrity and how efficiently it allows controlled water penetration and drug release. Unlike immediate-release or dispersible tablets, sustained-release systems are expected to resist rapid disintegration to maintain prolonged therapeutic activity.

In this study, the disintegration times for the Diclofenac sodium sustained-release tablets ranged from 394.33 ± 25.33 min (E1) to 25.60 ± 2.00 min (E10). The first five batches (E1–E5), formulated with Eudragit RL-100, PEG, and HPMC, showed significantly prolonged disintegration times (315–394 min). This can be attributed to the formation of a viscous gel layer by HPMC, which together with the hydrophobic Eudragit, restricted water penetration and tablet erosion, thereby prolonging matrix integrity.

In contrast, batches 6–10, where HPMC was replaced with maize starch mucilage, exhibited much shorter disintegration times (65.17 ± 2.14 min to 25.60 ± 2.00 min). The significant reduction in disintegration time is linked to the highly hydrophilic and swelling nature of maize starch mucilage, which enhances capillary water uptake and tablet breakup. As the proportion of starch mucilage increased, the matrix became less compact and more prone to controlled erosion rather than gel formation, facilitating faster water ingress. This observation supports earlier findings that native and modified starches can act as efficient disintegrants and release modifiers in matrix systems when combined with hydrophobic polymers like Eudragit.

Overall, the results clearly demonstrate that replacing HPMC with maize starch mucilage converted the matrix from a primarily gel-controlled system to a swelling-erosion-controlled one, resulting in faster disintegration. Thus, the polymeric combination of Eudragit RL-100, PEG, and HPMC mucilage achieved a desirable result for sustained-release Diclofenac formulations.

3.3.5 DISSOLUTION TIME

Before conducting the dissolution studies, a standard calibration curve for pure Diclofenac sodium was prepared in order to establish the relationship between concentration and absorbance at 278 nm. The absorbance values obtained for known concentrations were subjected to linear regression analysis to generate the calibration equation expressed as

$Y = MX + C$……..

Where;

Y = y-axis (Absorbance)

M = Slope

X = x-axis (concentration)

C = Intercept of curve on the y-axis

Such that the equation of the straight line (Y = MX + C) is

$Y = 0.0003x + 0.0006$

The correlation coefficient (r^2) was 0.988.

The percentage drug released per unit time was calculated using the formula:

$M_t/M_0 \times 100$……

Where;

M_0 = Amount of Drug

M_t = Amount of Drug released at time t.

M_t = Concentration of drug × Dissolution factor × Volume of diluent

The standard calibration curve of Diclofenac sodium in the HCL and Phosphate

Buffer Medium gave a straight line, indicating that Beer–Lambert's law was obeyed within the concentration range used. This law states that the absorbance of a monochromatic light beam passing through a homogeneous solution is directly proportional to the concentration of the absorbing species and the path length.

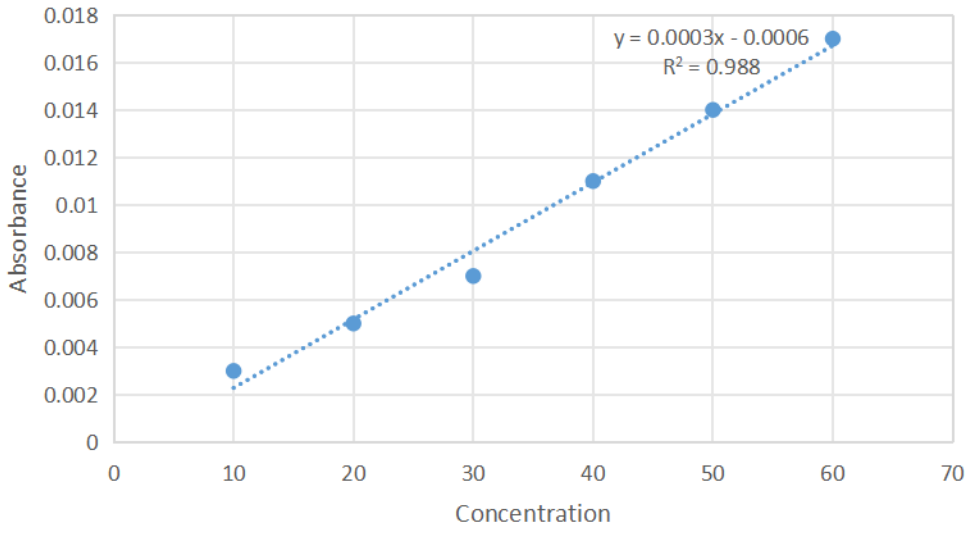

Figure 3.2 Standard Calibration plot of Diclofenac Sodium (Phosphate Buffer)

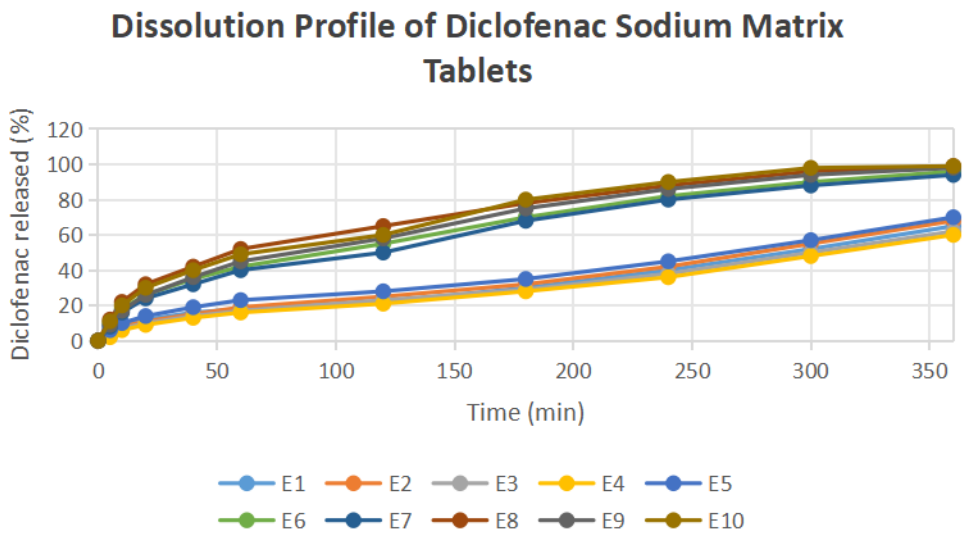

Figure 3.2: Dissolution profile of Sustained-Release Diclofenac tablets.

Overall, the dissolution profiles showed a clear difference between the HPMC-based batches (E1–E5) and the maize-starch–based batches (E6–E10) across both media and time points. In 0.1 N HCl (0–120 minutes), all batches released only a small fraction of Diclofenac, but the HPMC formulations were the slowest, with E1–E5 releasing roughly 16–28% of drug after 2 hours. In contrast, the maize starch mucilage batches had already released much more drug at the same time, with E6–E10 reaching about 35–55% at 120 minutes. This indicates that HPMC formed a tighter gel matrix in the acidic medium, restricting drug diffusion and helping to minimise premature gastric release.

When the medium was changed to phosphate buffer (simulating intestinal conditions, 180–360 minutes), the difference between both groups became even more evident. By 3–4 hours (180–240 minutes), the maize-starch formulations (E6–E10) had released between about 70 and 90% of the drug, approaching complete dissolution by 6 hours (360 minutes), where values were close to 96–100%. In contrast, the HPMC-based batches E1–E5 showed a slower, more gradual increase in release over the same period, reaching only about 65–70% by 6 hours.

Taken together, these results show that the maize starch mucilage blends produced a faster and more complete drug release, whereas the HPMC blends produced a slower, more controlled profile. This supports the conclusion that HPMC is more suitable for achieving sustained release of Diclofenac sodium, while maize starch mucilage behaves more like a release-accelerating excipient that would be better suited for immediate- or moderately fast-release matrix systems rather than for prolonged release.

CHAPTER 4

4.0 CONCLUSION

This study investigated the effect of a blend of hydrophilic polymers on drug release from Diclofenac sodium matrix tablets. Ten batches were prepared using Eudragit RL-100 and different combinations of PEG, HPMC, and maize starch mucilage. Batches 1–5 contained Eudragit, PEG, and HPMC, while batches 6–10 contained Eudragit, PEG, and maize starch mucilage.

All formulated tablets complied with official pharmacopoeial limits for weight uniformity, friability, and hardness, confirming acceptable mechanical quality. However, significant differences were observed in disintegration and release behavior based on the hydrophilic polymer used. The HPMC-based formulations exhibited the highest hardness (6.5–6.9 kg/cm^2), lowest friability (≤ 0.2 %), and the longest disintegration times (315–394 min), indicating the formation of a strong gel matrix capable of maintaining structural integrity and achieving prolonged drug release.

Conversely, replacing HPMC with maize starch mucilage resulted in weaker tablets with shorter disintegration times (65–25 min). The rapid water uptake and swelling properties of maize starch led to faster tablet erosion and loss of matrix integrity, which is undesirable for sustained-release purposes. While PEG improved the cohesion and wetting of the tablets, it did not slow drug release as effectively as HPMC.

The study suggests that HPMC remains a superior hydrophilic polymer for achieving sustained drug release in Diclofenac matrix tablets due to its gel-forming and diffusion-controlling

properties. The inclusion of maize starch mucilage may be more suitable for immediate-release systems rather than for sustained-release formulations.

The results affirm that the type and proportion of hydrophilic polymer play a critical role in determining the mechanical and release characteristics of matrix tablets, and careful optimization is required to achieve a desirable balance between structural strength and prolonged drug release.

4.1 RECOMMENDATIONS

I recommend the use of a blend of HPMC and PEG in the formulation of sustained-release diclofenac tablets, as it has proven to reduce tablet disintegration time.

Further study is also recommended to unravel the negative effect of maize starch mucilage on sustained-release formations.

4.2 LIMITATIONS

Despite the promising findings, this study had several limitations that warrant consideration:

i. **Variability in environmental factors**: Factors such as humidity and temperature, could influence the reproducibility of the results in different settings.

ii. **The use of old equipment:** The use of old equipment could introduce bias and result in variability.

iii. **Lack of adequate Power supply**: The Laboratory work was carried out with an allocation of only 5 hours a day of electricity to the lab on most days. This not only prolonged the study but also increased the cost of carrying out the study.

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