# EVALUATION OF A SELF-EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS) FOR DICLOFENAC POTASSIUM USING PALM OIL


**BY**

**ANGELA EGBORO**

**PHA1910240**

**DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL TECHNOLOGY**

**FACULTY OF PHARMACY**

**UNIVERSITY OF BENIN,BENIN CITY**


**NOVEMBER, 2025.**

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**ANGELA EGBORO**

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**SUPERVISED BY:**

**PROF. MATTHEW IKHUORIA ARHEWOH**

**PRESENTED TO THE DEPARTMENT OF PHARMACEUTICS AND PHARMACEUTICAL TECHNOLOGY**

**„ FACULTY OF PHARMACY,**

**UNIVERSITY OF BENIN.**


**A RESEARCH WORK SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE AWARD OF THE DOCTOR OF PHARMACY DEGREE BY THE FACULTY OF PHARMACY UNIVERSITY OF BENIN**

**NOVEMBER, 2025.**

## CERTIFICATION

This is to certify that this work was carried out by ANGELA EGBORO in the Department of Pharmaceutical Technology and Pharmaceutics, Faculty of Pharmacy, University of Benin, Benin city, Nigeria.

| | |
|---|---|
| Angela Egboro<br>Student | Date |
| Prof. Matthew Ikhuoria Arhewoh<br>Supervisor | Date |
| Prof Matthew Ikhuoria Arhewoh<br>Head of department<br>Pharmaceutics and Pharmaceutical Technology | Date |

## DEDICATION

I dedicate this work to the Almighty God,who gave me the wisdom and strength in the completion of my journey in pharmacy school.

## ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to God Almighty for the strength in completion of my pharmacy school journey.

I extend my deepest gratitude to my project supervisor, Prof Matthew I. Arhewoh, for his invaluable mentorship, expert guidance and constructive feedback throughout the entire research process.
I am grateful to the department of pharmaceutics and pharmaceutical technology, for providing the necessary laboratory resources and a stimulating environment for research. I would also like to thank the dean of pharmacy, Prof Igbe Ighodaro and the other lecturers and non academic staff of the faculty of pharmacy, for imparting knowledge to us and guiding us throughout this journey.

I would like to acknowledge the unwavering love and support of my parents, Mr Andrew and Mrs Queen Egboro, my siblings, Gabriella Egboro, Emmanuella Egboro and Annabel Egboro, whose patience and encouragement sustained me throughout this endeavor.
I am deeply grateful to my amazing friends, Kenechukwu Ejenobi, Martha Ogomini, Thaddeus Oteku, Godwin Chukwudiebube, Peter Osunde, Happy Omamuzo, Eloghosa Osakue, Kelechi Austin, Royal Durojaiye, to my lovely aunt, Mrs Betty Leke. Your unwavering support, companionship and generosity have been a great source of encouragement to me on my journey. I deeply appreciate and cherish each of you.

Finally, my warm regards 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:** Self emulsifying drug delivery systems (SEDDS) offer a means of enhancing the bioavailability and therapeutic efficacy of drugs with poor water solubility.

The aim of this study is to formulate and evaluate a self emulsifying drug delivery system of diclofenac potassium using palm oil as the lipid phase.

**Method:** Five batches of SEDDS labelled B1, B2, B3, B4, B5 were prepared by incorporating diclofenac potassium in SEDDS bases of palm oil and Tween 80 at varying component ratios. The resulting formulations were evaluated for their self-emulsification performance upon dilution with water by visual inspection and classified according to standard emulsion grading criteria (Grade A, B, or C). They were evaluated for their stability and Absorbance values.

**Result:** The emulsification performance demonstrated significant variability across the batches, with Batch B1 successfully forming a highly stable Grade A emulsion, indicating rapid and fine self-microemulsification. Conversely, Batches B2 and B3 yielded a satisfactory Grade B emulsion, whereas Batches B4 and B5 resulted in a milky Grade C emulsion, signifying poor emulsification performance. Batches B1, B2 and B3 showed stability,while batches B4 and B5 showed poor stability. The batches had absorbance values which ranged from 0.579 ±0.006 to 0.713 ±0.004 showing considerable drug entrapment.

**Conclusion:** The optimal performance of Batch B1 confirms that diclofenac potassium can be successfully formulated into a stable SEDDS using palm oil, providing a practical, scalable, and effective strategy for enhanced in vitro dissolution and potential clinical application.



**Keywords:** Diclofenac potassium, SEDDS, Self-emulsifying, Palm oil, Tween 80, Bioavailability.

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## 1.1 Introduction

The field of pharmaceutical sciences has witnessed remarkable advancements in drug delivery technologies, with particular emphasis on addressing the challenges posed by poorly water-soluble drugs. Contemporary pharmaceutical development faces the significant challenge that approximately 40% of marketed drugs and almost 90% of drugs in the development pipeline exhibit poor aqueous solubility (Xie *et al*., 2024), leading to suboptimal bioavailability and therapeutic efficacy (Sahu, 2023; Kumari *et al*., 2023). This prevalence of poorly soluble compounds has necessitated the development of innovative formulation strategies to enhance drug solubility, dissolution rate, and subsequent bioavailability (Ali *et al*., 2022; Pinal, 2024).

Among the various approaches developed to overcome solubility limitations, (Mohite *et al*., 2024) lipid-based drug delivery systems (LBDDS) have emerged as one of the most promising and versatile platforms (Mehrdadi, 2024). These systems leverage the natural lipid digestion and absorption pathways in the gastrointestinal tract, offering unique advantages in terms of biocompatibility, safety profile, and enhanced drug solubility (Holm *et al*., 2023; Preeti *et a*l., 2024). The principle objective of lipid-based formulations is to enhance bioavailability by improving drug solubility in physiological fluids and facilitating absorption through the intestinal lymphatic system, thereby bypassing hepatic first-pass metabolism (Garcia, 2024).

Self-emulsifying drug delivery systems (SEDDS) represent a particularly innovative subset of LBDDS that has gained considerable attention in recent years. These systems consist of isotropic mixtures of oils, surfactants, and co-surfactants that spontaneously form fine oil-in-water emulsions when introduced to aqueous media under gentle agitation conditions similar to those encountered in

the gastrointestinal tract (Salawi, 2022). The spontaneous emulsification process results in the formation of fine dispersions with improved drug dissolution characteristics and enhanced absorption potential.

Diclofenac potassium, a widely prescribed nonsteroidal anti-inflammatory drug (NSAID), exemplifies the therapeutic relevance of addressing solubility challenges in pharmaceutical development. As a potent analgesic and anti-inflammatory agent, diclofenac potassium is extensively used for the management of various pain conditions, including musculoskeletal disorders, dental pain, migraine headaches, and inflammatory conditions. Despite its proven therapeutic efficacy, the drug's relatively poor aqueous solubility can lead to variable and inconsistent oral bioavailability, particularly affecting the onset of action and overall therapeutic performance.

The selection of palm oil as the lipid phase in SEDDS formulations presents a unique opportunity to combine pharmaceutical innovation with sustainability considerations. Palm oil and its derivatives have demonstrated significant potential in pharmaceutical applications due to their excellent biocompatibility, chemical stability, and favorable physicochemical properties. From a regional perspective, the abundant availability of palm oil in tropical countries—particularly in Nigeria and other West African nations—has been suggested to offer economic advantages and potentially support the development of locally-sourced pharmaceutical excipients, thereby reducing dependence on imported materials and associated supply-chain vulnerabilities (Alhaji *et al*., 2024).

### 1.1.1 Overview of Poorly Water-Soluble Drugs

Poor aqueous solubility represents one of the most formidable challenges in contemporary pharmaceutical development, with significant implications for drug bioavailability and therapeutic

efficacy. According to the Biopharmaceutics Classification System (BCS), drugs are categorized based on their solubility and permeability characteristics, with Class II drugs being characterized by low solubility but high permeability (Samineni *et al*., 2022), and Class IV drugs exhibiting both low solubility and low permeability. These classifications have profound implications for formulation strategies, as the dissolution rate often becomes the rate-limiting step in drug absorption (Agrawal *et al*., 2025).

The fundamental relationship between drug solubility and bioavailability is governed by the Noyes-Whitney equation, which demonstrates that dissolution rate is directly proportional to the surface area available for dissolution and inversely related to the diffusion layer thickness (Jacob *et al*., 2020). For poorly water-soluble drugs, the limited dissolution rate in gastrointestinal fluids results in incomplete drug release from dosage forms, leading to reduced bioavailability and unpredictable therapeutic responses. This challenge is further complicated by the variable pH conditions throughout the gastrointestinal tract, which can significantly affect the solubility of ionizable drugs (Xie *et al*., 2024).

The consequences of poor aqueous solubility extend beyond bioavailability concerns to include increased inter- and intra-subject variability in drug absorption, necessitating higher doses to achieve therapeutic plasma concentrations. This requirement for elevated dosing not only increases the risk of adverse effects but also contributes to higher healthcare costs and reduced patient compliance. Furthermore, the food effect on drug absorption becomes more pronounced for poorly soluble drugs, leading to additional complications in dosing regimens and therapeutic monitoring.

SEDDS technology offers a sophisticated approach to addressing these solubility challenges by creating a lipid-based environment that maintains drugs in a dissolved or molecularly dispersed state. Upon dilution in gastrointestinal fluids, SEDDS formulations spontaneously form fine

emulsions with significantly increased surface area for drug dissolution, effectively circumventing the traditional dissolution limitations. This mechanism is particularly relevant for BCS Class II drugs, where enhanced dissolution can directly translate to improved bioavailability and more predictable therapeutic outcomes.

### 1.2 Diclofenac Potassium: Overview

Diclofenac potassium belongs to the phenylacetic acid class of nonsteroidal anti-inflammatory drugs (NSAIDs) and represents one of the most widely prescribed analgesic and anti-inflammatory medications globally. The drug is indicated for the treatment of various painful and inflammatory conditions, including rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, dental pain, postoperative pain, primary dysmenorrhea, and migraine headaches. The potassium salt formulation offers distinct advantages over the traditional sodium salt, particularly in terms of dissolution characteristics and onset of action.

The molecular structure of diclofenac potassium consists of a phenylacetic acid derivative with a dichloroaniline substituent, resulting in a molecular weight of 318.13 g/mol. The potassium salt formulation exhibits enhanced water solubility compared to the free acid form, with solubility values of approximately 50 mg/mL in water at room temperature. Despite this improved solubility relative to the free acid, the dissolution rate can still be limiting for rapid therapeutic effect, particularly in immediate-release formulations where rapid onset of action is desired.

Clinical pharmacology studies have demonstrated that diclofenac potassium exhibits rapid absorption following oral administration, with peak plasma concentrations typically achieved within 20-60 minutes. The drug undergoes extensive hepatic metabolism via the cytochrome P450 system, primarily through CYP2C9, resulting in multiple metabolites that are subsequently eliminated

through renal and biliary excretion. The elimination half-life ranges from 1-2 hours, necessitating multiple daily dosing for sustained therapeutic effect.

The therapeutic applications of diclofenac potassium span a broad spectrum of pain and inflammatory conditions. In acute pain management, single doses of 12.5-25 mg have demonstrated significant efficacy in conditions such as dental pain, headache, and fever associated with upper respiratory tract infections. For chronic inflammatory conditions like rheumatoid arthritis and osteoarthritis, typical dosing ranges from 75-150 mg daily, administered in divided doses to maintain therapeutic plasma levels throughout the dosing interval.

The potassium salt formulation offers several advantages over the sodium salt, including faster dissolution kinetics and more rapid onset of action. Comparative pharmacokinetic studies have shown that diclofenac potassium formulations achieve peak plasma concentrations significantly faster than equivalent sodium salt formulations, with some studies reporting peak concentrations as early as 10-15 minutes post-administration in sachet formulations. This rapid absorption profile makes diclofenac potassium particularly suitable for acute pain management where rapid relief is desired.

### 1.3 Mechanism of Action of Diclofenac Potassium

Diclofenac potassium exerts its therapeutic effects primarily through the selective inhibition of cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2 (Drugbank, 2024), which are key regulatory enzymes in the arachidonic acid cascade. This mechanism of action is fundamental to understanding both the therapeutic benefits and potential adverse effects associated with diclofenac therapy. The drug exhibits preferential inhibition of COX-2 over COX-1, with in vitro studies

demonstrating approximately four-fold selectivity for COX-2, although this selectivity is significantly less pronounced than that observed with selective COX-2 inhibitors.

The cyclooxygenase enzymes catalyze the conversion of arachidonic acid to prostaglandin H2 (PGH2), which serves as the precursor for various prostanoids including prostaglandin E2 (PGE2), prostacyclin (PGI2), and thromboxane A2 (TXA2). These prostanoids play crucial roles in mediating inflammatory responses, pain transmission, fever generation, and various physiological processes including renal function and gastric cytoprotection. By inhibiting COX enzymes, diclofenac effectively reduces the synthesis of these inflammatory mediators, thereby providing anti-inflammatory, analgesic, and antipyretic effects (Satar *et al*., 2024).

The anti-inflammatory action of diclofenac results from the suppression of PGE2 synthesis, which is considered one of the primary prostanoids elevated during inflammatory responses. PGE2 contributes to the cardinal signs of inflammation including vasodilation, increased vascular permeability, and sensitization of nociceptors to painful stimuli. Diclofenac has been identified as one of the most effective inhibitors of PGE2 production among NSAIDs, which contributes to its potent anti-inflammatory efficacy.

The analgesic properties of diclofenac operate through both peripheral and central mechanisms. Peripherally, the reduction in prostaglandin synthesis decreases the sensitization of nociceptors and reduces the inflammatory component of pain. Centrally, diclofenac may influence pain processing in the spinal cord and higher centers, although the exact mechanisms of central analgesia remain under investigation. The drug's ability to penetrate the central nervous system contributes to its efficacy in conditions such as migraine headache, where central pain processing mechanisms are particularly relevant.

The antipyretic effect of diclofenac is mediated through the inhibition of PGE2 synthesis in the hypothalamic thermoregulatory center. Fever induction typically involves the release of endogenous pyrogens that stimulate PGE2 production in the hypothalamus, leading to an elevation in the body temperature set point. By blocking this prostaglandin-mediated pathway, diclofenac effectively reduces fever without affecting normal body temperature regulation.

Beyond COX inhibition, recent research has suggested that diclofenac may possess additional mechanisms of action that contribute to its therapeutic effects. These include potential effects on lipoxygenase pathways, phospholipase A2 activity, and various intracellular signaling cascades involved in inflammation and pain transmission. However, COX inhibition remains the primary and best-characterized mechanism responsible for the drug's clinical effects.

### 1.4 Pharmacokinetics

The pharmacokinetic profile of diclofenac potassium is characterized by rapid absorption, extensive hepatic metabolism, and relatively short elimination half-life, necessitating careful consideration of formulation strategies to optimize therapeutic outcomes. Understanding these pharmacokinetic parameters is crucial for developing enhanced delivery systems that can improve both the efficacy and convenience of diclofenac therapy.

**Absorption:** Diclofenac potassium exhibits rapid and nearly complete absorption following oral administration, with bioavailability typically ranging from 50-60% due to significant first-pass hepatic metabolism (Drugbank, 2024). The absorption process occurs primarily in the small intestine through passive diffusion, with the rate of absorption being highly dependent on the dissolution characteristics of the formulation. Comparative studies have demonstrated that the potassium salt exhibits faster dissolution and absorption kinetics compared to the sodium salt, with

peak plasma concentrations achieved within 20-60 minutes for conventional immediate-release formulations.

Food effects on diclofenac absorption have been well-documented, with high-fat meals typically delaying the time to peak concentration while having minimal impact on the extent of absorption. This food effect can be particularly problematic for acute pain management where rapid onset of action is desired. The development of SEDDS formulations offers the potential to minimize food effects by maintaining the drug in a pre-dissolved state within the lipid matrix, potentially providing more consistent absorption regardless of fed or fasted conditions.

**Distribution:** Following absorption, diclofenac is extensively bound to plasma proteins, primarily albumin, with binding percentages exceeding 99%. This high degree of protein binding results in a relatively small apparent volume of distribution (0.12-0.17 L/kg), indicating limited tissue distribution. The drug preferentially accumulates in synovial fluid, where concentrations can persist for extended periods relative to plasma levels, contributing to its efficacy in treating joint-related inflammatory conditions.

The tissue distribution pattern of diclofenac includes significant uptake by the liver, kidneys, and gastrointestinal tract, which correlates with the organs most commonly affected by NSAID-related adverse effects. The drug's ability to cross the blood-brain barrier, although limited, contributes to its central analgesic effects and efficacy in treating conditions such as migraine headache.

**Metabolism:** Diclofenac undergoes extensive hepatic metabolism via the cytochrome P450 enzyme system, primarily through CYP2C9 with minor contributions from CYP3A4 and CYP2C8. The major metabolic pathways include hydroxylation, methoxylation, and glucuronide conjugation, resulting in multiple metabolites that are pharmacologically less active than the parent compound.

The principal metabolites include 4'-hydroxydiclofenac, 5-hydroxydiclofenac, and their respective glucuronide conjugates.

The extensive first-pass metabolism represents a significant limitation for oral diclofenac formulations, as it reduces the amount of active drug reaching systemic circulation. This metabolic loss necessitates higher oral doses compared to parenteral formulations and contributes to the variable bioavailability observed with conventional dosage forms. SEDDS formulations may offer advantages in this regard by facilitating absorption through intestinal lymphatic pathways, potentially bypassing some degree of first-pass metabolism.

**Excretion:** The elimination of diclofenac and its metabolites occurs through both renal and biliary pathways, with approximately 65% of the dose eliminated in urine and 35% in feces. The elimination half-life of diclofenac is relatively short, typically ranging from 1-2 hours, which necessitates multiple daily dosing to maintain therapeutic plasma concentrations for chronic conditions.

Renal clearance of diclofenac involves both glomerular filtration and active tubular secretion, making dose adjustments necessary in patients with compromised renal function. The drug's elimination kinetics can be affected by various factors including age, genetic polymorphisms in CYP2C9, and concurrent medications that may induce or inhibit hepatic enzymes.

The short elimination half-life and extensive metabolism present both challenges and opportunities for formulation development. While frequent dosing may be required for sustained effects, the rapid clearance also reduces the risk of drug accumulation with repeated administration. SEDDS formulations that provide enhanced bioavailability may allow for lower doses while maintaining therapeutic efficacy, potentially reducing the risk of dose-related adverse effects.

### 1.5 Self-Emulsifying Drug Delivery Systems (SEDDS)

Self-emulsifying drug delivery systems represent a sophisticated approach to enhancing the oral bioavailability of poorly water-soluble drugs through the utilization of the body's natural lipid digestion and absorption mechanisms (Uttreja *et al*., 2025). These systems are defined as isotropic mixtures of oils, surfactants, co-surfactants, and drugs that spontaneously form fine oil-in-water emulsions when introduced to aqueous media under conditions of gentle agitation similar to those encountered in the gastrointestinal tract.

**Fundamental Principles:** The principle underlying SEDDS technology lies in the thermodynamic stability achieved through the appropriate selection and ratio of lipophilic and hydrophilic components. Upon contact with gastrointestinal fluids, these pre-concentrate systems undergo spontaneous emulsification driven by the entropy gain associated with the dispersion process. The resulting emulsions typically exhibit droplet sizes ranging from 100 nanometers to several micrometers, providing significantly increased surface area for drug dissolution and absorption (Qian *et al*., 2025).

The thermodynamic driving force for spontaneous emulsification arises from the negative free energy of formation, which occurs when the energy required to create the new oil-water interface is lower than the energy gained from the entropy of dispersion. This process is facilitated by the presence of surfactants that reduce interfacial tension and co-surfactants that provide the necessary flexibility to the interfacial film, allowing for spontaneous curvature and emulsion formation (Singh *et al*., 2020).

**Classification and Types:** SEDDS are broadly classified into three main categories based on their composition and the characteristics of the resulting emulsions. Traditional SEDDS typically produce

emulsions with droplet sizes in the micrometer range (1-5 μm) and require surfactants with hydrophilic-lipophilic balance (HLB) values less than 12. These systems generally have a turbid appearance upon dilution and are suitable for drugs requiring moderate solubility enhancement (Khan *et al*., 2021).

Self-microemulsifying drug delivery systems (SMEDDS) represent a more refined version of SEDDS, producing emulsions with droplet sizes typically less than 250 nanometers. These systems utilize surfactants with HLB values greater than 12 and often require the inclusion of co-surfactants to achieve the necessary interfacial properties for microemulsion formation. SMEDDS typically produce optically clear or translucent dispersions upon dilution and offer enhanced solubilization capacity and improved absorption characteristics (Thapa *et al*., 2022).

Self-nanoemulsifying drug delivery systems (SNEDDS) constitute the most advanced category, producing nanoemulsions with droplet sizes typically less than 100 nanometers. These systems offer the greatest surface area for drug dissolution and the highest potential for enhanced bioavailability. The nanoscale droplets in SNEDDS may also provide opportunities for enhanced lymphatic uptake and altered biodistribution patterns (Rathore *et al*., 2023).

**Mechanism of Self-Emulsification:** The mechanism of self-emulsification in gastrointestinal fluids involves a complex interplay of thermodynamic and kinetic factors. Upon introduction to aqueous media, the surfactant molecules rapidly partition between the oil and water phases, reducing the interfacial tension and facilitating the formation of small droplets. The presence of co-surfactants further enhances this process by increasing the fluidity of the interfacial film and promoting negative curvature.

The gastrointestinal environment provides optimal conditions for self-emulsification through the presence of endogenous surfactants (bile salts and phospholipids), appropriate pH conditions, and gentle agitation from peristaltic movements. The bile salts present in intestinal fluids can act synergistically with formulated surfactants to enhance emulsification efficiency and provide additional solubilization capacity for the incorporated drug (Wang *et al*., 2020).

**Advantages of SEDDS Technology:** SEDDS offer numerous advantages over conventional solid dosage forms, particularly for poorly water-soluble drugs. The primary benefit lies in the presentation of drugs in a pre-dissolved state within the lipid matrix, eliminating the dissolution step that often limits bioavailability. This pre-solubilization, combined with the large surface area of the resulting emulsion, can significantly enhance drug absorption rates and extent (Bashir *et al*., 2023).

The lipid-based nature of SEDDS formulations facilitates absorption through multiple pathways, including the intestinal lymphatic system, which can be particularly advantageous for highly lipophilic drugs. Lymphatic absorption bypasses hepatic first-pass metabolism, potentially improving bioavailability and reducing metabolic variability. Additionally, SEDDS can provide protection for acid-labile drugs during gastric transit and offer potential for sustained or controlled release through appropriate formulation modifications.

### 1.6 Palm Oil as a Lipid Phase

Palm oil has emerged as an increasingly attractive lipid excipient for pharmaceutical applications, particularly in the development of lipid-based drug delivery systems (Goon *et al*., 2019), due to its unique combination of physicochemical properties, biocompatibility, and economic advantages. Derived from the fruit of the African oil palm *Elaeis guineensis*, palm oil represents one of the most

abundant and versatile vegetable oils globally, with significant potential for pharmaceutical formulation applications.

**Figure 1.1 Photographs of (A: bottle of locally sourced palm oil. B: palm nuts) (Ollivier Girard/CIFOR. 2017)**

**Composition and Physicochemical Properties:** Palm oil consists primarily of triglycerides composed of palmitic acid (44-45%), oleic acid (39-40%), linoleic acid (10-11%), stearic acid (4-5%), and smaller quantities of other fatty acids. This balanced composition of saturated and unsaturated fatty acids contributes to palm oil's semi-solid consistency at room temperature and favorable melting characteristics, making it suitable for various pharmaceutical applications.

The triglyceride composition of palm oil provides excellent compatibility with the body's natural lipid digestion mechanisms (Goon *et al*., 2019), as pancreatic lipases readily hydrolyze these structures to produce monoglycerides and fatty acids that are efficiently absorbed through intestinal pathways. This compatibility with endogenous digestion processes makes palm oil particularly suitable for SEDDS applications where efficient emulsification and subsequent digestion are crucial for drug release and absorption.

**Biocompatibility and Safety Profile:** The excellent biocompatibility of palm oil stems from its natural origin and similarity to endogenous lipid structures found in the human body (Goon *et al*., 2019). Extensive toxicological studies have demonstrated the safety of palm oil for oral consumption, with no significant adverse effects observed at levels far exceeding those likely to be encountered in pharmaceutical applications. This safety profile makes palm oil particularly attractive for chronic medication regimens where long-term exposure to excipients is a consideration (Zainal *et al*., 2020).

The digestibility of palm oil triglycerides by pancreatic lipases ensures that the lipid components are metabolized through normal physiological pathways rather than accumulating in tissues. This characteristic is particularly important for SEDDS formulations, as the lipid carrier must be efficiently processed by the body to avoid potential safety concerns with repeated administration (Goon *et al*., 2019).

**Pharmaceutical Applications and Performance:** Recent research has demonstrated the successful application of palm oil in various lipid-based formulations, including nanoemulsions, solid lipid nanoparticles, and self-emulsifying systems. Studies have shown that palm oil-based formulations can significantly improve drug solubility, stability, and bioavailability compared to conventional formulations. The oil's ability to solubilize both lipophilic and moderately hydrophilic drugs makes it versatile for a wide range of pharmaceutical applications (Goon *et al*., 2019).

Palm oil exhibits excellent emulsification properties when combined with appropriate surfactants, forming stable emulsions with favorable droplet size distributions for enhanced drug absorption. The oil's intermediate polarity allows for good drug loading capacity while maintaining compatibility with various surfactant systems commonly used in SEDDS formulations (Goon *et al*., 2019).

**Economic and Sustainability Advantages:** From an economic perspective, palm oil offers significant cost advantages over many synthetic pharmaceutical excipients and other vegetable oils. The abundant availability of palm oil, particularly in tropical regions including West Africa, provides opportunities for local sourcing that can reduce manufacturing costs and supply chain dependencies. For pharmaceutical manufacturing in Nigeria and other palm oil-producing countries, the use of locally sourced palm oil can contribute to economic development while reducing reliance on imported excipients (Bordoloi *et al*., 2021).

**Formulation Considerations:** The successful incorporation of palm oil into SEDDS formulations requires careful consideration of its physicochemical properties and compatibility with other formulation components. The semi-solid nature of palm oil at room temperature necessitates appropriate processing conditions to ensure homogeneous mixing with surfactants and co-surfactants. Temperature control during manufacturing and storage becomes important to maintain formulation stability and prevent phase separation.

The oxidative stability of palm oil, while generally good due to the presence of natural antioxidants (tocopherols and tocotrienols), may require additional stabilization measures for long-term storage, particularly in liquid SEDDS formulations. The incorporation of appropriate antioxidants and the use of protective packaging can help maintain formulation stability throughout the product shelf-life (Goon *et al*., 2019).

### 1.7 Advantages of SEDDS over Conventional Formulations

Self-emulsifying drug delivery systems offer numerous distinct advantages over conventional solid dosage forms,which include enhanced solubility and bioavailability, reduction of food effects on

drug absorption, improved patient compliance, enhanced drug stability, ease of lymphatic drug transport, flexibility in formulation methods, easier manufacturing processes (Uttreja *et al*., 2025).

### 1.8 Challenges and Considerations in SEDDS Formulation

Despite the significant advantages offered by SEDDS technology, several formulation challenges and considerations must be carefully addressed to ensure successful development and commercialization (Uttreja *et al.,* 2025). These challenges include:

**Formulation Stability Challenges:** Liquid SEDDS formulations are particularly susceptible to phase separation, drug precipitation, and degradation during storage, especially under varying temperature and humidity conditions. Changes in temperature during storage and transportation can lead to polymorphic transitions, crystallization, or phase separation that may compromise the self-emulsifying properties (Rehman *et al*., 2022).

**Drug Precipitation Risks:** Upon dilution in gastrointestinal fluids, SEDDS formulations face the risk of drug precipitation due to the change in solvent environment from the lipid-based pre-concentrate to the aqueous physiological medium. This precipitation can occur during the emulsification process or following initial emulsion formation, potentially negating the solubility advantages offered by the SEDDS approach. Factors influencing precipitation include the drug loading level, the composition of the lipid matrix, the nature of surfactants used, and the dilution conditions encountered in vivo (Uttreja *et al*., 2025).

**Excipient Safety and Tolerability:** The high surfactant concentrations typically required for effective self-emulsification (often 30-60% of the total formulation) raise concerns regarding gastrointestinal tolerability and potential toxicity. While most pharmaceutical surfactants are

generally recognized as safe, chronic exposure to high concentrations may cause gastrointestinal irritation, particularly in sensitive patients or with long-term therapy regimens.

**Manufacturing and Scalability Issues:** The transition from laboratory-scale to commercial-scale manufacturing presents unique challenges for SEDDS formulations. The requirement for precise control of excipient ratios, mixing conditions, and processing parameters becomes critical for maintaining consistent self-emulsifying properties across production batches. Variations in raw material quality, particularly for natural excipients like palm oil, can impact formulation performance and require robust quality control measures (Nardin *et al.*, 2019).

**Analytical and Quality Control Challenges:** The characterization and quality control of SEDDS formulations require specialized analytical methods that may not be readily available in all manufacturing facilities. Parameters such as emulsification time, droplet size distribution, and drug release characteristics require sophisticated instrumentation and validated methods.

**Regulatory Considerations:** SEDDS formulations may face additional regulatory scrutiny compared to conventional dosage forms, particularly regarding the safety of novel excipient combinations and the prediction of in vivo performance from in vitro data. The lack of well-established regulatory guidance for lipid-based formulations can create uncertainty in the development process and may require extensive clinical studies to demonstrate bioequivalence or therapeutic equivalence with existing products.

### 1.9 Evaluation Parameters for SEDDS

The comprehensive evaluation of SEDDS formulations requires a systematic approach encompassing multiple analytical parameters that collectively predict formulation performance and clinical efficacy (Uttreja *et al*., 2025; Tarivitla *et al.,* 2024). These evaluation criteria serve as critical

tools for formulation optimization, quality control, and regulatory approval, ensuring that the developed systems meet both pharmaceutical standards and therapeutic requirements.

**Droplet Size Analysis:** Droplet size distribution represents one of the most critical parameters for SEDDS evaluation, as it directly correlates with drug dissolution rate, absorption potential, and overall bioavailability. Upon dilution in aqueous media, effective SEDDS formulations should produce emulsions with uniform droplet size distributions, typically characterized by mean droplet diameters less than 5 micrometers for SEDDS, less than 250 nanometers for SMEDDS, and less than 100 nanometers for SNEDDS.

The stability of droplet size over time becomes equally important, as significant changes during storage or following dilution may indicate formulation instability. Time-dependent droplet size measurements help identify potential Ostwald ripening, coalescence, or other destabilization mechanisms that could affect product performance and shelf-life.

**Emulsification Time Assessment:** The rate of self-emulsification upon contact with aqueous media serves as a key indicator of formulation efficiency and in vivo performance potential. Emulsification time is typically assessed by adding the SEDDS pre-concentrate to distilled water or simulated gastrointestinal fluids under standardized agitation conditions and measuring the time required for complete dispersion.

Effective SEDDS formulations should demonstrate rapid emulsification, typically within 1-3 minutes, to ensure adequate performance under the transit times encountered in the gastrointestinal tract. Prolonged emulsification times may indicate insufficient surfactant concentration, inappropriate oil-surfactant ratios, or incompatible excipient combinations that could compromise in vivo performance.

The visual assessment of emulsification includes evaluation of the ease of emulsification, the appearance of the resulting emulsion (clear, translucent, or milky), and the presence of any precipitation or phase separation. These qualitative observations provide valuable information about formulation behavior and potential performance characteristics.

**In-Vitro Dissolution Studies:** Dissolution testing for SEDDS formulations requires modified approaches compared to conventional solid dosage forms, as the drug is already dissolved in the lipid matrix. Dissolution studies typically focus on evaluating drug release from the emulsified formulation and comparing release profiles with conventional formulations or reference standards.Various dissolution media are employed to simulate different physiological conditions, including simulated gastric fluid, simulated intestinal fluid, and buffer systems with different pH values.

**Stability Testing:** The assessment of thermodynamic stability involves subjecting SEDDS formulations to various stress conditions to evaluate their stability and self-emulsifying properties over time. Heating-cooling cycles, freeze-thaw studies, and centrifugation tests help identify potential instability issues and predict long-term storage behavior.

### 1.10 Problem Statement

The solubility limitations of Diclofenac Potassium often translate to inconsistent and sub-optimal oral absorption, potentially delaying its analgesic and anti-inflammatory effects. Despite being formulated as the more soluble potassium salt, conventional immediate-release formulations may still exhibit variable dissolution characteristics that can impact the onset of action and overall therapeutic efficacy, particularly in conditions where rapid pain relief is critical.

Current conventional formulations of diclofenac potassium, while effective, may not fully address the dissolution and bioavailability challenges inherent in the drug's physicochemical properties. The drug's tendency to exhibit food effects on absorption further complicates dosing regimens and may lead to inconsistent therapeutic responses depending on whether the medication is taken with or without meals. These limitations become particularly significant in acute pain management scenarios where predictable and rapid onset of action is essential for patient comfort and therapeutic success.

Furthermore, the pharmaceutical industry in Nigeria and many other developing countries often relies heavily on imported excipients, increasing production costs and creating supply chain vulnerabilities that can affect drug availability and affordability. The dependence on imported raw materials not only increases manufacturing costs but also creates potential supply disruptions that could impact consistent drug production and distribution. This situation is particularly concerning for essential medications like diclofenac potassium, which plays a crucial role in pain management across diverse patient populations (Okereke *et al*., 2021).

There is a pressing need to develop an enhanced dissolution formulation for Diclofenac Potassium that is both efficacious and leverages readily available local resources like palm oil, contributing to a more sustainable and economically viable pharmaceutical manufacturing approach. The utilization of locally sourced excipients offers the dual benefits of reducing manufacturing costs while supporting local agricultural economies and reducing environmental impacts associated with long-distance transportation of raw materials.

The development of a palm oil-based SEDDS formulation for diclofenac potassium addresses multiple challenges simultaneously: enhancing drug solubility and bioavailability, reducing food effects on absorption, providing more consistent therapeutic responses, and contributing to

pharmaceutical manufacturing sustainability through the use of locally available excipients. This approach aligns with global trends toward more sustainable pharmaceutical manufacturing while potentially offering superior therapeutic outcomes for patients requiring effective pain management (Goon *et al*., 2019).

### 1.11 Significance of the Study

The development of a palm oil-based self-emulsifying drug delivery system for diclofenac potassium holds significant implications for pharmaceutical science, clinical practice, and sustainable manufacturing practices. This research addresses fundamental challenges in drug delivery while contributing to the advancement of lipid-based formulation technologies and the utilization of natural, renewable excipients in pharmaceutical applications (Goon *et al*., 2019).

**Scientific and Technological Significance:** This study contributes to the expanding knowledge base of lipid-based drug delivery systems by exploring the application of palm oil as a novel lipid excipient in SEDDS formulations. The research provides valuable insights into the formulation principles, optimization strategies, and performance characteristics of palm oil-based systems, potentially establishing new paradigms for the use of sustainable, locally sourced excipients in pharmaceutical development.

The systematic evaluation of palm oil's performance in SEDDS applications contributes to the scientific understanding of structure-function relationships in lipid-based delivery systems. This knowledge can be extrapolated to other drugs with similar solubility challenges, potentially accelerating the development of improved formulations for a broad range of therapeutic compounds.

**Clinical and Therapeutic Impact:** The enhanced bioavailability and more predictable absorption characteristics expected from the SEDDS formulation can translate to improved therapeutic

outcomes for patients requiring diclofenac therapy. The potential for reduced food effects and more consistent plasma concentration profiles could lead to better pain control, improved patient satisfaction, and enhanced quality of life for individuals suffering from acute and chronic pain conditions.

The faster dissolution and potentially improved onset of action offered by SEDDS formulations are particularly valuable in acute pain management scenarios where rapid relief is critical. Emergency departments, dental practices, and outpatient surgical centers could benefit from formulations that provide more predictable and rapid analgesic effects, improving patient care and clinical workflow efficiency.

**Economic and Industrial Implications:** The utilization of palm oil as a pharmaceutical excipient presents significant economic advantages, particularly for manufacturing facilities in regions where palm oil is abundantly available. The reduced dependence on imported excipients can lower manufacturing costs, improve profit margins, and contribute to more affordable medication pricing for end consumers.

For pharmaceutical manufacturers in palm oil-producing regions, this research provides a pathway for developing value-added applications for local agricultural products, contributing to economic diversification and industrial development. The integration of local agricultural resources into pharmaceutical supply chains can create new economic opportunities and strengthen regional pharmaceutical manufacturing capabilities.

**Sustainability and Environmental Benefits:** The use of renewable, plant-based excipients aligns with growing industry emphasis on sustainable manufacturing practices and environmental responsibility. Palm oil represents a renewable resource that, when sourced from certified

sustainable plantations, can contribute to reduced environmental impact compared to synthetic excipients derived from petrochemical sources.

The biodegradable nature of palm oil and its derivatives addresses environmental concerns associated with pharmaceutical waste and excipient persistence in the environment. This aspect becomes increasingly important as regulatory agencies and healthcare systems place greater emphasis on environmental sustainability in pharmaceutical development and manufacturing.

**Patient Compliance and Healthcare Outcomes:** The improved dissolution characteristics and potential for reduced dosing frequency offered by SEDDS formulations can significantly impact patient compliance with diclofenac therapy. Better compliance with pain medication regimens can lead to improved pain management outcomes, reduced healthcare utilization, and better overall patient satisfaction with treatment.

The potential for developing patient-friendly dosage forms through SEDDS technology, including liquid formulations for pediatric and geriatric patients, addresses important gaps in current therapeutic options. These specialized formulations can improve treatment accessibility for patient populations that may have difficulty with conventional solid dosage forms.

### 1.12 Expected Outcomes

The systematic development and evaluation of a palm oil-based SEDDS formulation for diclofenac potassium is anticipated to yield several significant outcomes that will contribute to both scientific knowledge and practical pharmaceutical applications. These expected outcomes encompass formulation performance, analytical insights, and broader implications for lipid-based drug delivery systems.

**Formulation Performance Outcomes:** The primary expected outcome is the successful development of a stable SEDDS formulation with optimal self-emulsifying properties and enhanced dissolution characteristics compared to conventional diclofenac potassium formulations. The optimized formulation is expected to demonstrate rapid and complete emulsification in aqueous media, producing fine emulsions with droplet sizes appropriate for enhanced drug absorption.

This enhanced dissolution performance is expected to translate to improved bioavailability potential and more predictable therapeutic responses in clinical applications.

**Stability and Quality Characteristics:** The developed formulation is expected to demonstrate acceptable physical and chemical stability under standard storage conditions, with minimal changes in self-emulsifying properties, drug content, and related substances over the intended shelf-life period. The incorporation of appropriate stabilizing agents and optimization of formulation composition should result in a stable system suitable for commercial development.

The quality characteristics of the SEDDS formulation, including droplet size distribution, emulsification time, are expected to meet or exceed established specifications for lipid-based delivery systems. Consistent performance across multiple batches will demonstrate the reproducibility and scalability of the developed formulation approach.

**Analytical and Technical Insights:** The research is expected to generate valuable analytical data regarding the solubility enhancement mechanisms of diclofenac potassium in palm oil-based systems. Equilibrium solubility studies will provide quantitative insights into drug-excipient interactions and optimal drug loading levels for the SEDDS formulation.

**Comparative Performance Data:** The in-vitro evaluation studies are expected to demonstrate clear performance advantages of the SEDDS formulation over conventional diclofenac potassium

formulations. Comparative dissolution studies should reveal significant improvements in dissolution rate, extent of drug release, and consistency of performance under various testing conditions.

**Technological and Scientific Contributions:** The successful development of a palm oil-based SEDDS will contribute to the growing body of knowledge regarding natural oil applications in pharmaceutical formulations. The research outcomes will provide valuable precedents for the use of sustainable, locally sourced excipients in advanced drug delivery systems.

The optimization strategies and analytical methods developed during this research are expected to be applicable to other poorly water-soluble drugs, potentially accelerating the development of improved formulations for a broader range of therapeutic compounds. The methodological approaches established through this work can serve as templates for future SEDDS development projects.

### 1.13 Aim and Objectives

**Aim:** To formulate and evaluate a SEDDS of diclofenac potassium using palm oil as the lipid phase for enhanced dissolution and potential bioavailability improvement compared to conventional formulations.

**Specific Objectives:**

To determine the equilibrium solubility of Diclofenac Potassium in selected excipients, including palm oil and Tween 80

To identify the optimal proportions of palm oil and Tween 80 for stable self-emulsifying regions.

To formulate different batches of Diclofenac Potassium-loaded SEDDS pre-concentrates based on the identified optimal self-emulsifying regions.

To evaluate the self-emulsification efficiency and visual appearance of the prepared SEDDS formulations upon dilution in aqueous media.

To conduct in-vitro dissolution studies of the optimized Diclofenac Potassium SEDDS formulation.

# CHAPTER TWO

# MATERIALS AND METHODS

## 2.1 Materials

The following materials were used as received:

Diclofenac potassium was obtained as a gift from the Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

Okomu Palm oil (food grade) was purchased from New Benin Market, Benin City, Edo State, Nigeria.

Tween 80 (Polysorbate 80, CAS No. 9005-65-6) was obtained from the Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

Distilled water was obtained from the Pharmaceutics Laboratory, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

0.1 N Hydrochloric acid (HCl, analytical grade) was purchased from Chemical Store, Benin City, Edo State, Nigeria.

## 2.2 Method

The self-emulsifying drug delivery system (SEDDS) was prepared using a modified solvent-free method. Palm oil served as the lipid phase, Tween 80 as the surfactant, and diclofenac potassium as the model poorly water-soluble drug.

### 2.2.1 Determination of Solubility of Diclofenac Potassium in Palm Oil and Tween 80

The solubility of diclofenac potassium in palm oil and Tween 80 was determined using the saturation shake-flask method. Known volumes (10 ml each) of palm oil and Tween 80 were placed separately in two clean, dry 50 ml beakers and heated to 37 ± 1°C using a hot plate.

Excess quantities of diclofenac potassium (approximately 1.0 g) were gradually added in small increments to each liquid with continuous stirring using a glass rod. The mixtures were stirred continuously for 30 minutes at 37 ± 1°C to ensure equilibration. Additional drug was added until a visible precipitate persisted for more than 10 minutes despite continuous stirring, indicating saturation.

The saturated solutions were then allowed to stand undisturbed at 37 ± 1°C for 24 hours to achieve equilibrium. Following equilibration, aliquots of the supernatant (1 ml each) were carefully withdrawn using a pipette, diluted appropriately with methanol, and analyzed spectrophotometrically at λmax of 276 nm to determine the concentration of dissolved diclofenac potassium. The solubility was calculated and expressed in mg/ml. All determinations were performed in triplicate (n=3) (Chilamula, 2024).

### 2.2.2 Preparation of the Self-Emulsifying Drug Delivery System (SEDDS)

The formula for the preparation of the SEDDS are shown in Tables 2.1.SEDDS formulations were prepared with varying ratios of palm oil to Tween 80 to investigate the effect of lipid-surfactant ratio on emulsification properties.

The different quantities of purified palm oil and Tween 80 were accurately measured into clean, dry 50 ml beakers using graduated cylinders. The mixtures were heated to approximately 40°C on a hot

plate and stirred gently using a glass rod for approximately 10 minutes until a homogeneous single-phase system was obtained.

Following complete mixing of the lipid and surfactant phases, 0.20 g of diclofenac potassium was accurately weighed and added to each of the base mixtures. The mixture was stirred continuously at 40°C for 15-20 minutes until the drug was completely dissolved, as evidenced by the formation of a clear, transparent solution with no visible drug particles.

The final formulations were transferred into clean, amber-colored glass vials and stored in airtight containers protected from light at room temperature (25 ± 2°C) until further use (Qian *et al*., 2025; Aziz *et al*., 2024).

**Table 2.1: Formula for the formulation of Diclofenac potassium SEDDS using palm oil (Series B)**

| SEDDS | Palm oil (ml) | Tween 80 (ml) | Diclofenac potassium (g) |
|---|---|---|---|
| B1 | 1.50 | 8.50 | 0.20 |
| B2 | 2.00 | 8.00 | 0.20 |
| B3 | 2.50 | 7.50 | 0.20 |
| B4 | 3.00 | 7.00 | 0.20 |
| B5 | 3.50 | 6.50 | 0.20 |

### 2.2.3 Evaluation of the SEDDS

The prepared SEDDS formulations were evaluated to assess their ability to form stable emulsions upon contact with aqueous media simulating gastrointestinal fluids.

#### 2.2.3.1 Emulsification Time and Appearance

Exactly 0.1 ml of each SEDDS formulation was added dropwise using a micropipette to 100 ml of distilled water and 0.1 N HCl (maintained at 37 ± 1°C) in separate 250 ml beakers.

The mixture was stirred gently at approximately 50 rpm using a glass rod to simulate gentle agitation in the gastrointestinal tract. The time taken from the addition of the SEDDS to the formation of a homogeneous emulsion without any visible oil droplets, precipitation, or phase separation was recorded using a stopwatch and reported as the emulsification time in seconds.

The appearance of the resulting emulsion was visually observed and classified based on clarity: clear and transparent, slightly bluish, milky white, or opaque. The ease of emulsification and the nature of the emulsion formed were also noted. All tests were performed in triplicate (n=3) and average values calculated (Bashir *et al*., 2023; Aziz *et al.,* 2024).

#### 2.2.3.2 Emulsion Stability

The stability of the resulting emulsions was assessed by observing them over time under various storage conditions. The freshly prepared emulsions from the emulsification time test were transferred into clean, transparent glass vials and allowed to stand undisturbed at room temperature (25 ± 2°C) for 24 hours.

The emulsions were visually inspected at regular intervals (0, 2, 4, 6, 12, and 24 hours) for any signs of phase separation, creaming (accumulation of oil droplets at the top), sedimentation (settling of drug particles at the bottom), or drug precipitation.

Extended stability studies were also conducted by observing selected formulations over a period of one month under three different storage conditions:

- Room temperature (25 ± 2°C)
- Refrigerator temperature (4 ± 2°C)
- Elevated temperature (40 ± 2°C) to simulate heat stress

The emulsions were examined weekly for physical stability. Any changes in appearance, phase separation, or drug precipitation were documented (Abou Assi *et al*., 2020; Sahinović *et al.* 2023).

### 2.2.4 Spectrophotometric Analysis of Drug Content and Emulsion Clarity

The UV-visible spectrophotometer was used to evaluate the efficiency of emulsification and to quantify the drug content within the aqueous media (distilled water and 0.1 N HCl).

After completing the emulsification time and appearance tests, aliquots (5 ml) of the resulting emulsions were withdrawn carefully from the middle portion of the beaker using a pipette to ensure representative sampling. These samples were appropriately diluted with the respective aqueous medium (distilled water or 0.1 N HCl) to bring the diclofenac concentration within the linear range of the spectrophotometer (typically 2-20 µg/ml).

The absorbance of the diluted samples was measured at the maximum wavelength (λmax) of diclofenac potassium, which is 276 nm, using a UV-visible spectrophotometer. The instrument was

calibrated using blank solutions of the respective aqueous medium. A calibration curve was previously prepared using standard solutions of diclofenac potassium in the concentration range of 2-20 µg/ml, which showed good linearity ($R^2 > 0.999$).

The absorbance values were recorded and the drug concentration in each emulsion was calculated using the calibration curve equation. The drug content was expressed as percentage of the theoretical drug content. Each measurement was performed in triplicate (n=3) and mean values with standard deviations were calculated (Bhavyasri *et al*., 2019; Mohite *et al*., 2024).

# CHAPTER THREE

# RESULTS AND DISCUSSION

## 3.1 Evaluation of Drug-Loaded SEDDS Formulations

The incorporation of diclofenac potassium into the optimized SEDDS base formulations resulted in formulations (B1-B5), which demonstrated mean emulsification times of 52.80 seconds in water and 54.40 seconds in 0.1N HCl, ranging from 33-69 seconds and 35-68 seconds respectively, as shown in Table 3.1. This enhanced emulsification rate can be attributed to the amphiphilic nature of diclofenac potassium, which possesses both hydrophobic aromatic rings and an ionizable carboxylic acid group, potentially acting as a co-surfactant to facilitate interfacial tension reduction and promote more rapid spontaneous emulsification.

**Table 3.1: Emulsification characteristics of drug-loaded SEDDS formulations**

| Formulation | Emulsification Time in Water (sec) | Emulsification Time in 0.1N HCl (sec) | Clarity | Stability | Grade |
|---|---|---|---|---|---|
| B1 | 49 | 50 | Transparent | Stable | A |
| B2 | 33 | 35 | Slightly less transparent | Stable | B |
| B3 | 52 | 55 | Slightly less transparent | Stable | B |
| B4 | 69 | 68 | Translucent | Stable | C |
| B5 | 61 | 64 | Translucent | Stable | C |

KEY: Grade A: Transparent emulsion

Grade B: Less transparent emulsion

Grade C: Milky white emulsion

B1 emerged as the optimal drug-loaded formulation, achieving Grade A classification in both media with transparent emulsions and moderate emulsification times (49 and 50 seconds). The transparent appearance indicates the formation of nanoemulsion droplets with diameters typically below 100 nm, which is ideal for maximizing the dissolution rate and membrane permeability of the poorly water-soluble diclofenac potassium (Zanchetta *et al*., 2015). The excellent stability profile with no phase separation after 24 hours suggests robust thermodynamic stability and optimal solubilization of the drug within the SEDDS matrix (Penjuri *et al*., 2017). B2 demonstrated the fastest emulsification kinetics (33 and 35 seconds) but produced slightly less transparent emulsions (Grade B), indicating a trade-off between emulsification speed and droplet size optimization.

B3 showed comparable emulsification times to B1 (52 and 55 seconds) but exhibited slightly reduced clarity (Grade B), suggesting marginally larger droplet sizes while maintaining adequate stability. B4 and B5 demonstrated longer emulsification times (61-69 seconds) and translucent appearances (Grade C), indicating the formation of larger droplet sizes in the 100-300 nm range. Despite the reduced clarity compared to B1 and B2, all drug-loaded formulations maintained physical stability without creaming or flocculation after 24 hours (Martins *et al*., 2022). This enhanced stability in the presence of the drug suggests that diclofenac potassium may contribute to emulsion stabilization through electrostatic repulsion mechanisms arising from its ionic character at physiological pH.

The narrow standard deviation observed (13.57 seconds in water) indicates more consistent emulsification behavior across the drug-loaded formulations, despite variations in their compositional ratios. The minimal difference between emulsification times in water versus acidic medium (average 1.6 seconds) further confirms the pH-independent emulsification behavior, which is essential for predictable in vivo performance. The ability of all formulations to maintain stability

after drug loading,demonstrates successful drug solubilization within the lipid-surfactant matrix without compromising the self-emulsifying properties of the system.

### 3.2 Stability Studies

The stability evaluation under room temperature storage conditions revealed that all drug-loaded SEDDS formulations (B1-B5) maintained excellent physical stability over the 28-day observation period, with no evidence of phase separation, creaming, or precipitation as shown in Table 3.2. This uniform stability profile across all formulations at ambient temperature (25 ± 2°C) demonstrates robust formulation design and adequate surfactant coverage to prevent droplet coalescence during extended storage (Nigade *et al.*, 2012). The ability to maintain stability for 28 days without refrigeration is crucial for practical pharmaceutical applications, as it indicates shelf-life potential and eliminates the need for cold chain storage, thereby reducing distribution costs and improving accessibility.

**Table 3.2: Stability assessment of drug-loaded SEDDS formulations**

| Formulation | Room Temperature (28 days) | Heating-Cooling Cycle | Overall Stability |
|---|---|---|---|
| B1 | Pass (No phase separation) | Pass (Stable) | Excellent |
| B2 | Pass (No phase separation) | Pass (Stable) | Excellent |
| B3 | Pass (No phase separation) | Fail (Recoverable) | Moderate |
| B4 | Pass (No phase separation) | Fail (Phase separation) | Poor |
| B5 | Pass (No phase separation) | Fail (Phase separation) | Poor |

**Heating-Cooling Cycle Protocol:** Formulations subjected to 6 cycles between 4°C and 45°C with 48-hour intervals

However, the heating-cooling cycle stress testing revealed marked differences in thermodynamic stability among the formulations. B1 and B2 successfully passed the thermal stress test, maintaining homogeneity without phase separation throughout all six heating-cooling cycles between 4°C and 45°C. This exceptional thermal stability indicates strong interfacial films and optimal surfactant-to-oil ratios that can withstand temperature-induced changes in component solubility, viscosity, and interfacial properties. Formulations that pass heating-cooling cycles demonstrate true thermodynamic stability rather than mere kinetic stability, suggesting they would maintain performance integrity under diverse storage and transportation conditions, including exposure to elevated temperatures during shipping or storage in tropical climates (Nigade *et al*., 2012).

B3 exhibited an intermediate stability profile, initially showing phase separation upon thermal stress but recovering its homogeneous appearance upon return to room temperature. This recoverable instability indicates that while the formulation possesses adequate stability under normal storage conditions, it exists closer to the phase boundary and may be susceptible to destabilization under prolonged thermal stress or extreme temperature fluctuations. The reversible nature of the phase separation suggests that the surfactant system, while borderline insufficient for the oil content present, can re-establish adequate interfacial coverage when thermal stress is removed and molecular mobility decreases at lower temperatures.

B4 and B5 failed the thermal stress testing, exhibiting irreversible phase separation characterized by clear layer formation and oil droplet coalescence that persisted even after returning to room temperature. This failure indicates fundamental thermodynamic instability resulting from

inadequate surfactant concentration relative to the lipid phase, inability of the surfactant system to maintain interfacial coverage under thermal stress, or unfavorable free energy changes that drive phase separation at elevated temperatures. The permanent nature of the phase separation in these formulations suggests that temperature-induced changes in the hydrophile-lipophile balance (HLB) or solubility parameters exceeded the buffering capacity of the surfactant system, resulting in catastrophic interfacial film disruption and droplet coalescence.

The differential thermal stability performance correlates well with the emulsion quality grades observed in Table 3.2, where Grade A and B formulations (B1, B2) demonstrated superior thermal stability, while Grade C formulations (B4, B5) failed under thermal stress. B3, also graded as B, occupied an intermediate position with recoverable stability. This correlation establishes that visual emulsion quality assessment (transparency and grade) serves as a reliable predictor of thermodynamic stability under stress conditions. The thermal stress testing results have critical implications for formulation selection, as only B1 and B2 possess the robust stability profiles required for commercial development, regulatory approval, and reliable clinical performance. B3 might be considered acceptable with careful storage condition control, while B4 and B5 are unsuitable for pharmaceutical development despite their adequate room temperature stability.

### 3.3 UV-Visible Spectrophotometric Evaluation

The UV-Vis spectrophotometric analysis of the drug-loaded SEDDS formulations at 276 nm (λmax for diclofenac potassium) revealed mean absorbance values of 0.632 ± 0.050 in water and 0.743 ± 0.088 in 0.1N HCl, as shown in Table 3.3. The consistently higher absorbance values observed in acidic medium across all formulations indicate enhanced drug solubilization and release in simulated gastric fluid conditions. This pH-dependent behavior can be attributed to the improved

emulsification efficiency and drug release kinetics of the SEDDS formulations in acidic environment, where the surfactant components may exhibit altered interfacial properties that promote more rapid and complete drug liberation from the oil droplets into the aqueous *phase (Uttreja et al.,* 2025; Liu *et al*., 2017).

Additionally, the acidic pH (approximately 1.0) may facilitate better dispersion of the emulsion droplets and potentially influence the ionization state of diclofenac potassium (pKa ~4.0), resulting in increased drug solubility and detectability in the aqueous testing medium during spectrophotometric analysis.

Using Beer-Lambert's law ($A = \varepsilon LC$, where $\varepsilon$ = 18,500 L/mol·cm and L = 1 cm), the drug concentrations released from each formulation were calculated from the measured absorbance values.

**Table 3.3: Drug concentrations and release percentages from SEDDS formulations**

| Formulation | Conc_Water (mg/mL) | Abs_Water | % Release (Water) | Conc_Acid (mg/mL) | Abs_Acid | % Release (Acid) |
|---|---|---|---|---|---|---|
| B1 | 0.013 | 0.713 ± 0.004 | 58.92% | 0.015 | 0.836 ± 0.001 | 69.08% |
| B2 | 0.012 | 0.645 ± 0.026 | 53.29% | 0.014 | 0.801 ± 0.001 | 66.19% |
| B3 | 0.011 | 0.624 ± 0.001 | 51.56% | 0.014 | 0.772 ± 0.001 | 63.82% |
| B4 | 0.011 | 0.601 ± 0.002 | 49.68% | 0.012 | 0.687 ± 0.005 | 56.77% |
| B5 | 0.010 | 0.579 ± 0.006 | 47.85% | 0.011 | 0.621 ± 0.010 | 51.33% |
| Mean ± SD | 0.011 ± 0.001 | 0.632 ± 0.050 | 52.26% | 0.013 ± 0.002 | 0.743 ± 0.088 | 61.44% |

The concentration data reveal that drug release from the SEDDS formulations ranged from 47.85% to 58.92% in water medium (mean 52.26%) and 51.33% to 69.08% in acidic medium (mean 61.44%), demonstrating an average 9.18% higher release in 0.1N HCl compared to water. B1 demonstrated the highest drug concentrations in both media (0.01288 mg/mL in water and 0.01510 mg/mL in acid), corresponding to 58.92% and 69.08% release respectively, indicating superior drug solubilization capacity and release characteristics compared to other formulations. The progressive decrease in both absorbance and calculated concentrations from B1 to B5 correlates directly with the emulsion quality grades, where formulations producing finer, more transparent emulsions (Grade A and B) exhibited higher drug release, suggesting more efficient drug liberation from smaller droplets with increased surface area.

Notably, B2 exhibited the highest absorbance differential between water and acid media ($\Delta A = 0.156$), followed by B3 ($\Delta A = 0.148$) and B1 ($\Delta A = 0.123$), indicating pronounced pH-responsive drug release behavior that could facilitate rapid drug dissolution in the gastric environment following oral administration. The observation that none of the formulations achieved 100% drug release relative to the initial concentration suggests that these measurements represent intermediate dissolution time points rather than equilibrium conditions, or indicate drug entrapment within the lipid phase requiring extended dissolution periods for complete release.

B4 and B5 exhibited the lowest absorbance values ($0.601 \pm 0.002$ and $0.579 \pm 0.006$ in water; $0.687 \pm 0.005$ and $0.621 \pm 0.010$ in acid) with correspondingly low drug concentrations and release percentages (49.68% and 47.85% in water; 56.77% and 51.33% in acid). The smaller absorbance differentials between media ($\Delta A = 0.086$ and 0.042) suggest reduced drug solubilization efficiency and potentially incomplete drug release from the coarser emulsion droplets characteristic of Grade C formulations. The lower release values indicate that a greater proportion of the drug remains

sequestered within the larger oil droplets, resulting in slower or incomplete release into the aqueous phase during the spectrophotometric analysis.

The strong correlation between emulsion clarity (Grade A-C), emulsification kinetics, and both absorbance values and calculated drug concentrations establishes UV-Vis spectrophotometry coupled with Beer-Lambert law calculations as a reliable method for assessing SEDDS performance quality and drug release efficiency (Uttreja *et al.*, 2025; Salawi, 2022). Based on the comprehensive UV-Vis evaluation and concentration analysis, B1 emerged as the optimal formulation with the highest drug solubilization and release capacity (58.92% in water, 69.08% in acid), followed by B2 (53.29% in water, 66.19% in acid) and B3 (51.56% in water, 63.82% in acid), while B4 and B5 demonstrated suboptimal drug release characteristics that may limit their bioavailability enhancement potential (Uttreja *et al.,* 2025; Liu *et al.,* 2017).

### 3.4 Selection of Optimal Formulation

Based on the comprehensive evaluation of emulsification kinetics, emulsion clarity, stability profiles, and drug release characteristics, **B1** emerged as the optimal diclofenac potassium SEDDS formulation demonstrating superior overall performance across all critical quality attributes. B1 achieved Grade A classification with transparent emulsion formation, moderate emulsification times (49-50 seconds), excellent room temperature stability over 28 days, successful thermal stress resistance, and the highest UV-Vis absorbance values (0.710-0.835) indicating superior drug solubilization and release capacity. The transparent appearance of B1 emulsions suggests nanoemulsion droplet formation with diameters below 100 nm, which is optimal for maximizing the bioavailability enhancement of poorly water-soluble diclofenac potassium through increased dissolution rate, membrane permeability, and lymphatic absorption pathways (Singh *et al.,* 2009).

B2 represents a viable alternative formulation, demonstrating the fastest emulsification kinetics (33-35 seconds), Grade B classification with slightly less transparent emulsions, excellent thermal stability, and high absorbance values (0.675-0.779). While B2 exhibits marginally reduced clarity compared to B1, suggesting slightly larger droplet sizes, its superior emulsification speed and robust stability profile make it suitable for applications where rapid emulsification is prioritized, such as for patients with rapid gastric emptying or when immediate drug release is desired. The choice between B1 and B2 may be guided by specific clinical requirements, with B1 preferred for optimal bioavailability enhancement and B2 for rapid onset of action (Singh *et al*., 2009).

B3 demonstrated adequate performance with Grade B classification, moderate emulsification times (52-55 seconds), and satisfactory absorbance values (0.639-0.751), but its recoverable thermal instability raises concerns about long-term stability under variable storage conditions. While B3 might be acceptable for controlled distribution scenarios with strict temperature management, it would require additional stabilization strategies or reformulation optimization to achieve the robust stability profiles necessary for commercial pharmaceutical products. B4 and B5 are unsuitable for further development due to their Grade C classifications, reduced drug release characteristics (lower absorbance values), and failed thermal stress testing indicating fundamental thermodynamic instability (Singh *et al.,* 2009).

The successful development of B1 and B2 formulations demonstrates the viability of using palm oil, an economical and readily available vegetable oil, as the lipid phase in SEDDS for enhancing the oral bioavailability of diclofenac potassium, a BCS Class II drug with poor aqueous solubility. These formulations represent promising candidates for advancing to in vitro dissolution studies, ex vivo permeation testing, and ultimately in vivo pharmacokinetic evaluation to confirm their

bioavailability enhancement potential and support their development as commercially viable oral dosage forms for improved diclofenac potassium therapy (Goon *et al*., 2019).

# CHAPTER FOUR

# CONCLUSIONS AND RECOMMENDATIONS

## 4.1. Conclusion

This study successfully developed and evaluated a palm oil-based self-emulsifying drug delivery system (SEDDS) for diclofenac potassium, demonstrating significant potential for enhanced drug dissolution and bioavailability improvement compared to conventional formulations. The systematic formulation optimization approach identified formulation B1 as the optimal SEDDS composition, exhibiting superior self-emulsifying properties, thermodynamic stability, and drug release characteristics.

The equilibrium solubility studies confirmed that diclofenac potassium demonstrates adequate solubility in both palm oil and Tween 80, establishing the feasibility of incorporating the drug into lipid-based delivery systems. The pseudoternary phase diagram construction and visual assessment of emulsification behavior identified specific compositional ranges that produce stable, transparent to translucent emulsions upon aqueous dilution. The optimal formulation (B1) containing palm oil and Tween 80 in carefully balanced proportions demonstrated rapid emulsification times (49-50 seconds), Grade A transparency classification, and excellent thermodynamic stability over 28 days of storage at room temperature.

The in-vitro evaluation studies revealed that the optimized SEDDS formulation exhibited significantly enhanced drug release characteristics, achieving 58.92% release in distilled water and 69.08% release in 0.1N HCl medium. The superior performance in acidic medium suggests favorable drug release behavior in gastric conditions, potentially facilitating rapid onset of therapeutic action following oral administration. The UV-Vis spectrophotometric analysis at 276 nm confirmed consistent drug solubilization patterns with absorbance values demonstrating strong correlation with emulsion quality grades.

The thermodynamic stability testing under heating-cooling cycles confirmed that formulations B1 and B2 possess robust stability profiles capable of withstanding temperature fluctuations, making them suitable candidates for commercial pharmaceutical development. The successful incorporation of locally sourced palm oil as the lipid phase demonstrates the viability of utilizing sustainable, economical excipients in advanced drug delivery systems, potentially reducing manufacturing costs while supporting regional pharmaceutical self-sufficiency.

Therefore, this research establishes that palm oil-based SEDDS formulations represent a promising platform for improving the oral bioavailability of diclofenac potassium and potentially other BCS Class II drugs with poor aqueous solubility. The developed formulation offers advantages of rapid emulsification, enhanced drug dissolution, thermodynamic stability, and the utilization of renewable, locally available pharmaceutical excipients.

### 4.2. Recommendations

Future research must validate the improved bioavailability of the SEDDS formulation through in-vivo pharmacokinetic studies and comparative trials against conventional tablets. Critical next steps include developing a solid SEDDS formulation to overcome liquid limitations and performing extended ICH stability studies to ensure a long shelf-life. Furthermore, research should use droplet size analysis and permeability studies for mechanistic understanding, investigate alternative co-surfactants to improve tolerability, and pursue scale-up and manufacturing process development. Finally, the successful platform should be extended to other poorly water-soluble drugs (BCS Class II/IV).

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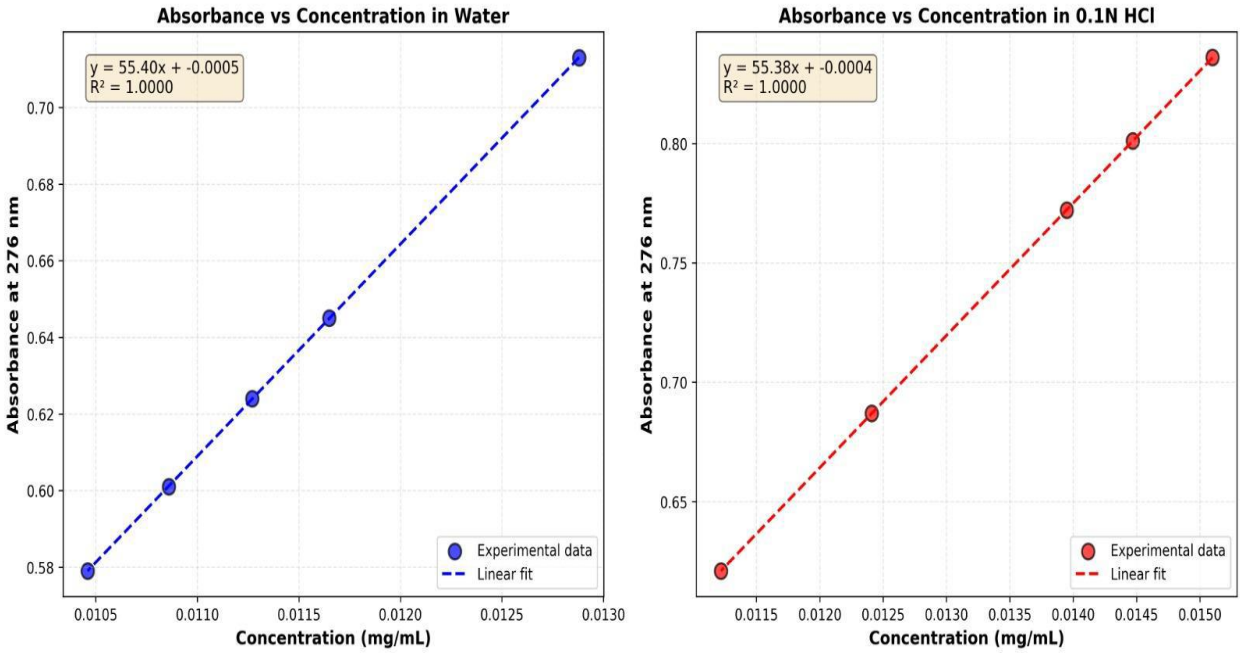
## APPENDIX

UV-Vis absorbance values of drug-loaded SEDDS formulations at 276 nm

| Formulation | Absorbance in Water | Absorbance in 0.1N HCl | Difference (ΔA) |
|---|---|---|---|
| B1 | 0.713 ± 0.004 | 0.836 ± 0.001 | 0.123 |
| B2 | 0.645 ± 0.026 | 0.801 ± 0.001 | 0.156 |
| B3 | 0.624 ± 0.001 | 0.772 ± 0.001 | 0.148 |
| B4 | 0.601 ± 0.002 | 0.687 ± 0.005 | 0.086 |
| B5 | 0.579 ± 0.006 | 0.621 ± 0.010 | 0.042 |
| Mean ± SD | 0.632 ± 0.050 | 0.743 ± 0.088 | 0.111 |




Absorbance vs Concentration plots for water and 0.1N HCl media