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Formulation and evaluation of nano emulsion of aceclofenac (100mg) for enhanced solubility and dissolution rate

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Abstract
Aceclofenac is a widely used non-steroidal anti-inflammatory drug (NSAID with proven efficacy in the management of pain and inflammatory disorders; however, its therapeutic performance is limited by poor aqueous solubility and dissolution rate, classifying it as a Biopharmaceutical Classification System (BCS) Class II drug. The present thesis focuses on the formulation and evaluation of a nanoemulsion-based drug delivery system of aceclofenac (100 mg) with the objective of enhancing its solubility and dissolution characteristics. Nanoemulsions were developed using suitable oils, surfactants, and co-surfactants through systematic screening and optimization techniques. The prepared formulations were characterized for critical quality attributes including droplet size, polydispersity index, zeta potential, drug content, pH, viscosity, and physical stability. In vitro dissolution studies were conducted to compare the release profile of the nanoemulsion formulation with that of pure aceclofenac and conventional formulations. The optimized nanoemulsion demonstrated nanoscale droplet size, good stability, uniform drug distribution, and a significantly enhanced dissolution rate. The improvement in dissolution behavior is attributed to increased surface area, enhanced solubilization of aceclofenac in the oil phase, and reduced diffusion path length associated with nanoemulsion droplets. The findings of this study confirm that nanoemulsion technology is an effective and promising approach for improving the solubility and dissolution rate of poorly water-soluble drugs like aceclofenac, with potential implications for enhanced oral bioavailability and improved therapeutic outcomes.
Keywords: Aceclofenac, Nanoemulsion, Solubility enhancement, Dissolution rate, Drug delivery system

INTRODUCTION

Overview of Drug Delivery Systems

The pharmaceutical industry has witnessed remarkable advancements in drug delivery systems over the past few decades, with a primary focus on improving the therapeutic efficacy and safety

of existing drugs [1]. Conventional drug delivery systems often face limitations such as poor bioavailability, erratic absorption, and unpredictable plasma concentration profiles, which compromise their therapeutic potential [2]. These challenges have driven researchers to explore novel delivery approaches that can overcome the inherent physicochemical limitations of drug molecules [3]. Among various strategies, nanotechnology-based delivery systems have emerged as a revolutionary approach, offering unprecedented opportunities to enhance drug solubility, stability, and bioavailability [4]. The development of nanoscale carriers has transformed the landscape of pharmaceutical formulation, particularly for drugs suffering from poor aqueous solubility [5].

The pharmaceutical significance of enhanced drug delivery cannot be overstated, as approximately 40% of marketed drugs and nearly 90% of molecules in the developmental pipeline exhibit poor water solubility [6]. This fundamental challenge affects the absorption profile, distribution, and ultimately the therapeutic outcome of many potentially effective pharmaceutical agents [7]. Traditional approaches to solubility enhancement, such as salt formation, co-solvency, and solid dispersion, have shown limited success and often introduce additional complexity in formulation development [8]. Consequently, the pharmaceutical research community has increasingly focused on nanotechnology-based solutions that can address these challenges more comprehensively and reliably [9].

Biopharmaceutical Classification System and Solubility Challenges

The Biopharmaceutical Classification System (BCS) was introduced by Amidon and colleagues as a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability [10]. This classification system has become instrumental in predicting the in vivo performance of drug products and guiding formulation development strategies [11]. According to the BCS, drugs are categorized into four distinct classes: Class I drugs exhibit high solubility and high permeability, Class II drugs show low solubility but high permeability, Class III drugs demonstrate high solubility but low permeability, and Class IV drugs possess both low solubility and low permeability [12].

Among these categories, BCS Class II drugs represent a particularly challenging group for pharmaceutical scientists, as their therapeutic efficacy is primarily limited by their dissolution rate rather than permeation characteristics [13]. The oral bioavailability of these drugs is dissolution-rate limited, meaning that enhancement of solubility and dissolution rate can significantly improve their absorption and therapeutic performance [14]. Statistical analyses reveal that approximately 60-70% of newly discovered drug candidates fall into BCS Class II, highlighting the magnitude of this pharmaceutical challenge [15]. The predominance of poorly water-soluble compounds in drug development pipelines necessitates innovative formulation strategies that can effectively address solubility limitations [16].

Nanoemulsion Technology: Principles and Advantages

Nanoemulsions represent a sophisticated class of colloidal dispersions characterized by droplet sizes typically ranging from 20 to 200 nanometers [21]. These systems are kinetically stable, transparent or translucent liquid dispersions of oil and water stabilized by an interfacial film of surfactant molecules [22]. Unlike conventional emulsions, nanoemulsions exhibit remarkable

stability against gravitational separation, flocculation, and coalescence due to their small droplet size and low interfacial tension [23].
The thermodynamic and kinetic stability of nanoemulsions distinguishes them from microemulsions, which are thermodynamically stable systems formed spontaneously [25]. While nanoemulsions require energy input for their formation, they demonstrate excellent long-term stability once prepared, making them more practical for large-scale pharmaceutical manufacturing [26]. The preparation of nanoemulsions typically involves high-energy methods such as high-pressure homogenization, ultrasonication, or microfluidization, which generate intense disruptive forces to break down oil droplets into the nanometer range [27].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
Non-steroidal anti-inflammatory drugs constitute one of the most widely prescribed classes of therapeutic agents globally, used extensively for their analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of NSAIDs primarily involves the inhibition of cyclooxygenase (COX) enzymes, which catalyze the conversion of arachidonic acid to prostaglandins and thromboxanes. Prostaglandins are lipid mediators that play crucial roles in inflammation, pain perception, fever, and various physiological processes including gastric mucosal protection and renal blood flow regulation. By blocking prostaglandin synthesis, NSAIDs effectively reduce inflammation, alleviate pain, and lower elevated body temperature.

The clinical applications of NSAIDs span a broad spectrum of conditions, including osteoarthritis, rheumatoid arthritis, acute musculoskeletal injuries, postoperative pain, dysmenorrhea, and various inflammatory disorders. Despite their widespread therapeutic utility, NSAIDs are associated with significant adverse effects, particularly gastrointestinal complications ranging from dyspepsia and gastric ulceration to potentially life-threatening bleeding and perforation. The gastrointestinal toxicity of NSAIDs results from both local irritation of the gastric mucosa and systemic inhibition of COX-1 enzyme, which is responsible for producing protective prostaglandins in the stomach lining. Cardiovascular and renal adverse effects have also been documented, particularly with long-term use or in susceptible patient populations.

REVIEW OF LITERATURE

Introduction

The development of novel drug delivery systems has been a subject of extensive research over the past few decades, driven by the need to overcome the limitations of

Aceclofenac: Pharmacological Profile and Therapeutic Applications
Aceclofenac is a phenylacetic acid derivative that belongs to the NSAID class, chemically designated as 2-[(2,6-dichlorophenyl)amino]phenylacetoxyacetic acid. This drug exhibits potent anti-inflammatory, analgesic, and antipyretic activities, making it valuable in the management of pain and inflammation associated with various musculoskeletal and joint disorders. Aceclofenac demonstrates preferential inhibition of COX-2 over COX-1, contributing to its favorable gastrointestinal safety profile compared to non-selective NSAIDs.

conventional formulations and improve therapeutic outcomes. Nanoemulsion technology has emerged as one of the most promising approaches for enhancing the solubility, dissolution rate,

and bioavailability of poorly water-soluble drugs. This chapter presents a comprehensive review of the literature pertaining to nanoemulsion formulations, their application in pharmaceutical drug delivery, and specifically their use for aceclofenac and other NSAIDs. The review encompasses fundamental aspects of nanoemulsion systems, formulation strategies, characterization techniques, and reported studies on solubility and bioavailability enhancement.

Fundamental Aspects of Nanoemulsion Systems

The concept of nanoemulsions as distinct colloidal systems was first recognized in the early 1990s, though emulsion technology itself has a much longer history in pharmaceutical sciences [31]. Researchers have distinguished nanoemulsions from conventional emulsions based on their unique characteristics including nanoscale droplet size, optical transparency or translucence, and enhanced kinetic stability [32]. The theoretical framework for understanding nanoemulsion formation and stability has evolved considerably, incorporating concepts from colloid science, interfacial chemistry, and thermodynamics.

Mason et al. investigated the mechanisms of droplet breakup during high-energy nanoemulsion preparation, demonstrating that turbulent flow, cavitation, and viscous shear forces contribute to the reduction of droplet size [33]. Their work established that the energy density input during homogenization directly correlates with the final droplet size achieved, with higher energy inputs generally producing smaller droplets up to a limiting minimum size determined by the surfactant system. The importance of surfactant dynamics during emulsification was highlighted, showing that rapid adsorption of surfactant to newly formed interfaces is crucial for stabilizing small droplets against immediate recoalescence.

Nanoemulsion Components and Selection Strategies

The selection of appropriate components for nanoemulsion formulations is critical for achieving optimal drug solubilization, system stability, and biopharmaceutical performance. Numerous studies have investigated the influence of different oils, surfactants, and co-surfactants on nanoemulsion properties and drug delivery applications.

Constantinides et al. examined various lipid excipients for their capacity to solubilize poorly water-soluble drugs and their behavior during formulation and in vivo digestion [36]. Their systematic screening approach identified medium-chain triglycerides, long-chain triglycerides, and various semi-synthetic glycerides as suitable oil phases for pharmaceutical nanoemulsions. The study emphasized that drug solubility in the oil phase is a primary determinant of achievable drug loading, while the digestibility of the oil influences the rate and extent of drug release and absorption in vivo.

Preparation Methods for Nanoemulsions

The methodologies employed for nanoemulsion preparation have been extensively studied, with researchers comparing the advantages and limitations of various high-energy and low-energy approaches.

Jafari et al. conducted comprehensive studies on high-pressure homogenization as a nanoemulsion preparation method, investigating the effects of processing parameters including homogenization pressure, number of cycles, and temperature [40]. Their research demonstrated

that pressures in the range of 500-1500 bar, applied over 3-10 homogenization cycles, effectively produce nanoemulsions with mean droplet sizes below 200 nm. The study also revealed that excessive homogenization can lead to droplet coalescence due to high collision frequencies, indicating an optimal processing window for each formulation system.

Characterization Techniques for Nanoemulsion Systems

Comprehensive characterization of nanoemulsion formulations is essential for understanding their properties, predicting stability, and ensuring consistent quality. Researchers have employed various analytical techniques and developed standardized protocols for nanoemulsion characterization.

Methodology

Rationale for the Study

Aceclofenac is a widely prescribed non-steroidal anti-inflammatory drug that has demonstrated significant clinical efficacy in the management of pain and inflammation associated with various musculoskeletal and rheumatic disorders. Despite its proven therapeutic benefits, the clinical utility of aceclofenac is compromised by its poor aqueous solubility, which classifies it as a Biopharmaceutics Classification System (BCS) Class II drug. This fundamental physicochemical limitation directly impacts the dissolution rate of the drug in gastrointestinal fluids, which in turn affects its absorption profile and overall bioavailability.

The aqueous solubility of aceclofenac is approximately 0.28 mg/mL, which is substantially inadequate for ensuring complete dissolution of the standard 100 mg therapeutic dose within the limited transit time through the gastrointestinal tract. This solubility limitation results in incomplete and variable drug absorption, leading to inter-individual and intra-individual variability in therapeutic response. The incomplete bioavailability necessitates administration of higher doses to achieve desired therapeutic plasma concentrations, which may increase the risk of dose-dependent adverse effects, particularly gastrointestinal complications that represent the most common limitation of NSAID therapy.

Conventional approaches to enhance the solubility of poorly water-soluble drugs, including particle size reduction through micronization, salt formation, solid dispersion, and complexation techniques, have been explored for aceclofenac with varying degrees of success. However, these traditional methods often suffer from significant limitations including physical instability during storage, tendency for particle aggregation, incomplete dissolution enhancement, manufacturing complexity, and inconsistent performance under physiological conditions. These shortcomings highlight the need for more advanced and robust formulation strategies that can reliably address the solubility and dissolution challenges associated with aceclofenac.

The development of aceclofenacnanoemulsion formulations offers the potential for significant improvements in drug solubility, dissolution rate, and ultimately bioavailability. Enhanced dissolution characteristics could translate to more rapid onset of therapeutic action, more consistent pharmacokinetic profiles across patient populations, potential for dose reduction while maintaining efficacy, and possibly improved gastrointestinal tolerability due to reduced local drug concentrations at the gastric mucosa. Furthermore, the liquid nature of nanoemulsion formulations provides advantages in terms of ease of administration, flexibility in dosing, and

potential for development into various final dosage forms including oral liquids, self-emulsifying capsules, or even topical preparations.

Aim of the Study

The primary aim of this research work is to formulate, optimize, and comprehensively evaluate nano emulsion systems containing aceclofenac (100 mg) for enhanced solubility and dissolution rate compared to pure drug and conventional formulations. This research aims to demonstrate the feasibility and advantages of nano emulsion technology for improving the biopharmaceutical properties of aceclofenac through systematic formulation development and comprehensive physicochemical characterization.

Specific Objectives

To achieve the stated aim, the following specific objectives have been established for this research work:

Solubility Studies To conduct systematic solubility screening of aceclofenac in various pharmaceutical oils including medium-chain triglycerides, long-chain triglycerides, oleic acid, isopropyl myristate, and other suitable lipid vehicles. This screening will identify oils providing maximum drug solubilization capacity, which is critical for achieving adequate drug loading in the final nanoemulsion formulation. The solubility data will guide the selection of the most appropriate oil phase for formulation development.

PLAN OF WORK

Overview of Research Plan

The research work will be conducted systematically following a well-defined sequence of activities designed to achieve the stated objectives. The plan encompasses preliminary studies, formulation development, optimization, characterization, and evaluation phases, with each phase building upon the results of previous activities.

Results and Discussion

Determination of λmax

The UV spectrum of aceclofenac in methanol showed maximum absorbance at 275 nm. This wavelength was selected for all subsequent analytical determinations.

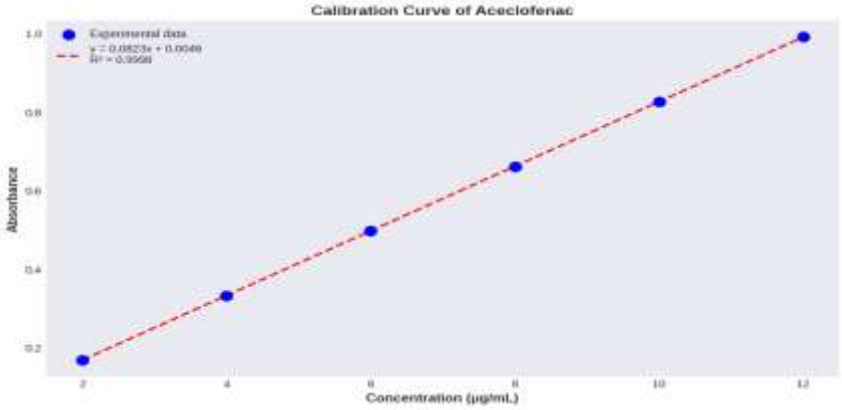
Calibration Curve

The calibration curve of aceclofenac showed excellent linearity in the concentration range of 2-12 µg/mL with regression equation: $y = 0.0823x + 0.0045$ and correlation coefficient (r^2) = 0.9998.

Table 6.1: Calibration Data for Aceclofenac

Concentration (µg/mL)	Absorbance (Mean ± SD, n=3)
2	0.169 ± 0.002
4	0.334 ± 0.003
6	0.498 ± 0.002
8	0.663 ± 0.004
10	0.827 ± 0.003

12	0.992 ± 0.005

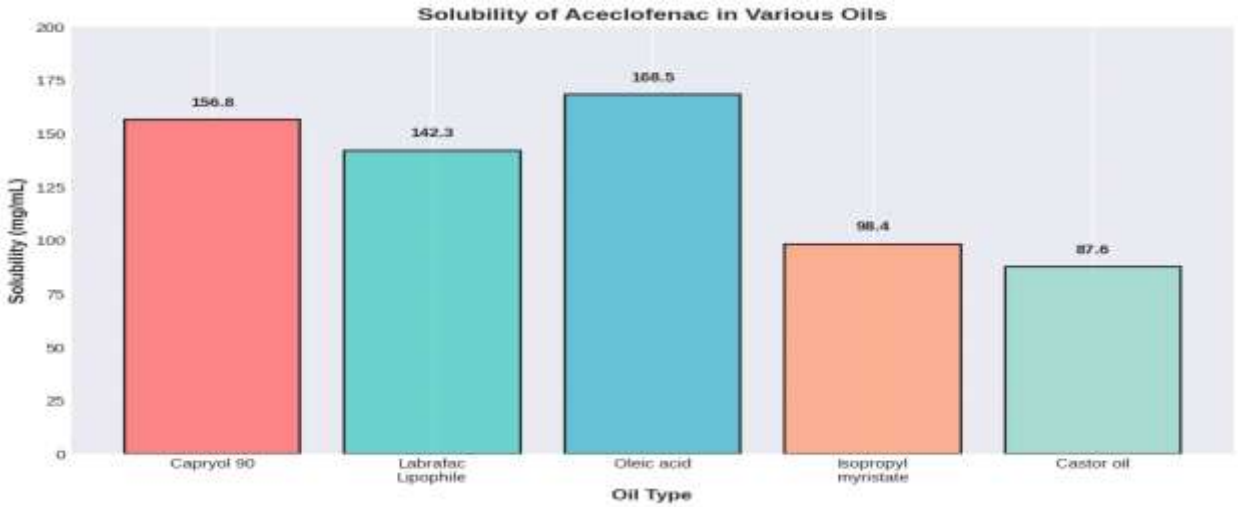


Method Validation Parameters

Table 6.2: Method Validation Parameters

Parameter	Result
Linearity range	2-12 µg/mL
Regression equation	y = 0.0823x + 0.0045
Correlation coefficient	0.9998
LOD	0.15 µg/mL
LOQ	0.45 µg/mL
Accuracy (% Recovery)	98.5-101.2%
Precision (%RSD)	
- Intraday	0.85%
- Interday	1.23%

The developed method demonstrated excellent linearity, accuracy, and precision, making it suitable for routine analysis of aceclofenac in nanoemulsion formulations.



Preformulation Studies

Physical Characteristics

Aceclofenac appeared as white to off-white crystalline powder, odorless with melting point of 150.5°C ± 1.2°C, which is in accordance with reported literature values.

Solubility Studies

Table 6.3: Solubility of Aceclofenac in Various Oils

Oil	Solubility (mg/mL) ± SD
Capryol 90	156.8 ± 4.2
Labrafac Lipophile	142.3 ± 3.8
Oleic acid	168.5 ± 5.1
Isopropyl myristate	98.4 ± 3.2
Castor oil	87.6 ± 2.9

Table 6.4: Solubility of Aceclofenac in Various Surfactants

Surfactant	Solubility (mg/mL) ± SD
Tween 80	78.5 ± 2.6
Tween 20	65.2 ± 2.1
Cremophor RH 40	82.3 ± 2.8
Span 80	45.6 ± 1.8

Table 6.5: Solubility of Aceclofenac in Various Co-surfactants

Co-surfactant	Solubility (mg/mL) ± SD
Transcutol P	92.4 ± 3.1
Propylene glycol	68.7 ± 2.4
PEG 400	72.3 ± 2.7
Glycerin	38.9 ± 1.5

Discussion: Oleic acid showed maximum solubility (168.5 mg/mL) among all tested oils, followed by Capryol 90 (156.8 mg/mL). However, considering the better emulsification properties and regulatory acceptance, Capryol 90 was selected as the oil phase for nanoemulsion formulation. Among surfactants, Cremophor RH 40 showed highest solubilization, while Transcutol P exhibited maximum solubility among co-surfactants. These components were selected for further formulation development.

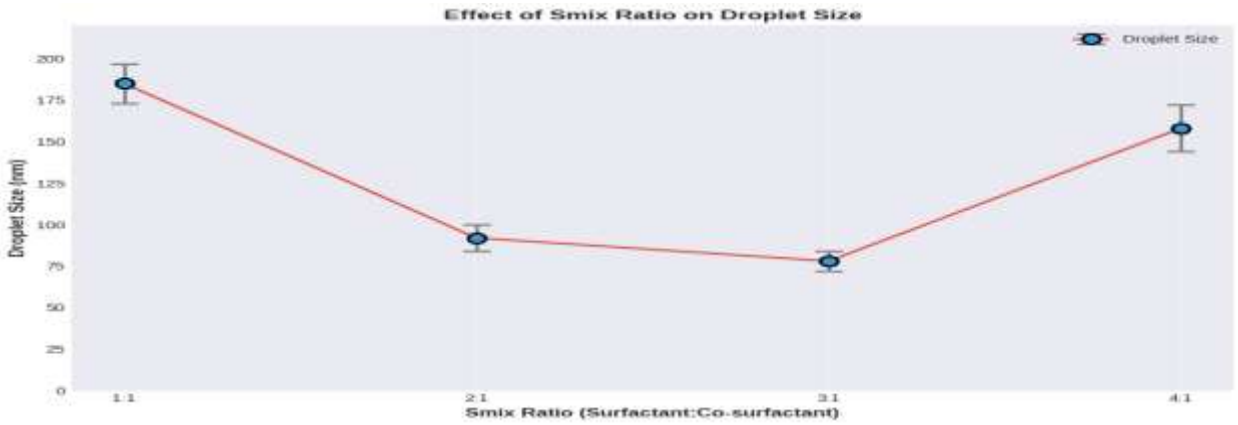
Drug-Excipient Compatibility Studies

FTIR spectra of pure aceclofenac showed characteristic peaks at 3318 cm^{-1} (N-H stretching), 1716 cm^{-1} (C=O stretching of carboxylic acid), 1773 cm^{-1} (C=O stretching of ester), 1587 cm^{-1} (aromatic C=C stretching), and 748 cm^{-1} (C-Cl stretching). The physical mixture of drug with selected excipients showed all characteristic peaks of aceclofenac without any significant shift or disappearance, indicating no incompatibility between drug and excipients.

Surfactant Selection Studies

Table 6.6: Effect of Smix Ratio on Emulsification Efficiency

Smix Ratio (S:CoS)	Spontaneous Emulsification	Droplet Size (nm)	Transparency
1:1	Good	185 ± 12	Translucent
2:1	Excellent	92 ± 8	Transparent
3:1	Excellent	78 ± 6	Transparent
4:1	Moderate	158 ± 14	Translucent



Discussion: The Smix ratio of 3:1 (Cremophor RH 40:Transcutol P) demonstrated excellent spontaneous emulsification with minimum droplet size (78 nm) and good transparency. This ratio was selected for construction of pseudoternary phase diagrams and further formulation development.

CONCLUSION

The present research successfully demonstrated the formulation and evaluation of a nanoemulsion system for aceclofenac (100 mg) as an effective strategy to overcome its poor aqueous solubility and dissolution limitations. The developed nanoemulsion exhibited nanosized droplet distribution, satisfactory stability, uniform drug content, and significantly enhanced in vitro dissolution compared to the pure drug.

The improved dissolution performance of aceclofenac from the nanoemulsion can be attributed to enhanced solubilization, increased interfacial surface area, and efficient stabilization provided by the surfactant system. These characteristics strongly suggest that nanoemulsion-based delivery can improve the oral bioavailability of aceclofenac and potentially reduce dose-related variability and gastrointestinal side effects associated with conventional formulations.

In conclusion, nanoemulsion technology represents a promising and viable formulation approach for BCS Class II drugs like aceclofenac. The outcomes of this study provide a strong foundation for further in vivo pharmacokinetic and bioavailability studies and support the potential development of nanoemulsion-based oral formulations for improved therapeutic effectiveness.

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