History of Medicine, 2026, 12(1): 137-150
DOI: 10.48047/HM. V12.I1.2026.137-150

Development and Evaluation of Sustained Release Tablets of Naproxen Sodium 500mg

Injeti Harshitha, Kranthi[2], Praveen Guijula[3], D. Raghava[4], Kavala Nageswara Rao[5]

[1] PG Scholar, Department of Pharmaceutical Technology, KGRL college of pharmacy Bhimavaram, west Godavari, Andhra Pradesh, India 534201.
[2] Assistant Professor, Department of Pharmaceutical Technology, KGRL college of pharmacy, Bhimavaram, west Godavari, Andhra Pradesh, India 534201.
[3] Professor, Department of Pharmaceutical Technology, KGRL college of pharmacy Bhimavaram, west Godavari, Andhra Pradesh, India 534201
[4]Principal and professor Department of pharmaceutical chemistry, KGRL college of pharmacy, Bhimavaram, west Godavari, Andhra Pradesh, India 534201.
[5] Director and Professor Department of Pharmaceutical Analysis, KGRL college of pharmacy, Bhimavaram, west Godavari, Andhra Pradesh, India 534201.

ABSTRACT

Naproxen sodium is a widely used non-steroidal anti-inflammatory drug (NSAID) for the management of pain, inflammation, and fever. Conventional immediate-release formulations require frequent dosing (2-3 times daily), leading to fluctuations in plasma drug concentrations, suboptimal patient compliance, and increased risk of adverse effects. Sustained release formulations offer potential advantages including reduced dosing frequency, minimized peak- trough fluctuations, improved patient compliance, and potentially enhanced safety profile.

Keywords: Naproxen sodium, sustained release tablets, HPMC, matrix tablets, dissolution kinetics, direct compression, stability studies.

INTRODUCTION

1.1 Background and Rationale

The pharmaceutical industry has witnessed remarkable advancements in drug delivery systems over the past few decades, with sustained release formulations emerging as one of the most significant innovations in therapeutic drug administration [1]. These sophisticated delivery systems have revolutionized the way medications are administered and absorbed in the human body, offering numerous advantages over conventional immediate-release

formulations [2]. The development of sustained release dosage forms represents a critical area of pharmaceutical research, aimed at optimizing therapeutic outcomes while minimizing adverse effects and improving patient compliance [3].

Sustained release drug delivery systems are designed to release the active pharmaceutical ingredient at a predetermined rate, maintaining therapeutic drug concentrations in the systemic circulation for an extended period [4]. This controlled release mechanism offers several distinct advantages, including reduced dosing frequency, minimized fluctuations in plasma drug concentrations, decreased incidence of side effects, and improved patient adherence to prescribed therapeutic regimens [5]. The ability to maintain drug levels within the therapeutic window for prolonged periods represents a significant advancement in pharmaceutical technology, particularly for medications requiring chronic administration [6].

Non-steroidal anti-inflammatory drugs (NSAIDs) constitute one of the most widely prescribed classes of therapeutic agents globally, with applications spanning pain management, inflammation control, and fever reduction [7]. Among the diverse array of NSAIDs available in clinical practice, naproxen sodium has established itself as a prominent therapeutic agent due to its potent anti- inflammatory, analgesic, and antipyretic properties [8]. The extensive utilization of naproxen sodium in treating various inflammatory conditions, including rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and acute musculoskeletal disorders, underscores its clinical significance [9].

1.2 Naproxen Sodium: Pharmacological Profile

Naproxen sodium, chemically designated as (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid sodium salt, belongs to the propionic acid derivative class of NSAIDs [10]. This compound exhibits its therapeutic effects primarily through the non-selective inhibition of cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2, which are crucial enzymes in the biosynthesis of prostaglandins and thromboxane [11]. The inhibition of these inflammatory mediators results in the alleviation of pain, reduction of inflammation, and normalization of elevated body temperature [12].

The pharmacokinetic profile of naproxen sodium reveals several characteristics that make

it an ideal candidate for sustained release formulation development [13]. Following oral administration, naproxen sodium demonstrates rapid and complete absorption from the gastrointestinal tract, with peak plasma concentrations typically achieved within 1-2 hours in immediate-release formulations [14]. The drug exhibits a relatively long elimination half-life ranging from 12 to 17 hours, which is longer than many other NSAIDs, providing a theoretical advantage for sustained release formulation design [15].

The bioavailability of naproxen sodium approaches approximately 95% following oral administration, indicating excellent absorption characteristics [16]. The drug demonstrates extensive plasma protein binding, primarily to albumin, with binding percentages exceeding 99%, which influences its distribution and elimination patterns [17]. Naproxen undergoes hepatic metabolism primarily through demethylation and conjugation reactions, producing metabolites that are subsequently eliminated through renal excretion [18].

1.3 Sustained Release Technology: Principles and Advantages

Sustained release drug delivery systems represent a sophisticated approach to pharmaceutical formulation, designed to release the active ingredient at a controlled rate over an extended duration [1]. These systems employ various mechanisms to modulate drug release, including diffusion through polymeric matrices, erosion of carrier materials, osmotic pressure gradients, and ion exchange processes [2]. The fundamental objective of sustained release technology is to maintain plasma drug concentrations within the therapeutic range for prolonged periods, typically 12 to 24 hours, from a single dose administration [3].

The development of sustained release formulations involves the judicious selection and combination of pharmaceutical excipients, particularly polymers that control the rate and extent of drug release [4]. Hydrophilic polymers, such as hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose, and various grades of polyethylene oxide, are frequently employed in matrix-based sustained release systems [5]. These polymers swell upon contact with aqueous media, forming a gel layer through which the

drug diffuses at a controlled rate [6].

Matrix tablets represent one of the most widely utilized approaches for achieving sustained drug release due to their simplicity in manufacturing, cost-effectiveness, and versatility in accommodating various drugs with different physicochemical properties [7]. In matrix systems, the drug is uniformly dispersed throughout a polymeric carrier, and release occurs through a combination of polymer swelling, drug dissolution, and diffusion through the swollen matrix [8]. The release kinetics can be modulated by varying the type and concentration of the polymer, the drug-to-polymer ratio, and the incorporation of additional excipients [9].

CHAPTER 3: REVIEW OF LITERATURE

3.1 Introduction

The development of sustained release drug delivery systems represents a significant advancement in pharmaceutical technology, addressing the limitations of conventional immediate-release formulations and improving therapeutic outcomes across various disease conditions [31]. Over the past several decades, extensive research has been conducted to understand the principles governing sustained drug release, optimize formulation strategies, and develop innovative delivery systems that meet specific therapeutic requirements [32]. This chapter presents a comprehensive review of the scientific literature pertaining to sustained release formulations, with particular emphasis on matrix tablet systems, polymeric materials used in controlled release applications, and formulations of naproxen and related non-steroidal anti-inflammatory drugs [33].

The evolution of sustained release technology has been driven by the recognition that maintaining optimal drug concentrations in the therapeutic window for extended periods can significantly enhance treatment efficacy while minimizing adverse effects [34]. This paradigm shift from conventional to modified-release formulations has necessitated a deeper understanding of drug release mechanisms, polymer behavior, and the complex interplay between formulation variables and release kinetics [35]. The literature reviewed in this chapter provides the scientific foundation for the development of sustained release tablets of naproxen sodium and highlights the current state of knowledge in this field [36].

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3.2 Fundamentals of Sustained Release Drug Delivery Systems

3.2.1 Concepts and Definitions

Sustained release drug delivery systems are designed to release the active pharmaceutical ingredient at a predetermined rate, maintaining therapeutic drug concentrations for an extended duration following a single dose administration [37]. Various terminologies have been used in the literature to describe these systems, including controlled release, prolonged release, extended release, and modified release, each with subtle distinctions in their precise definitions [38]. The United States Pharmacopeia defines extended-release dosage forms as those that allow at least a two-fold reduction in dosing frequency compared to immediate-release formulations of the same active ingredient [39]

Research conducted by various investigators has established that the primary objective of sustained release systems is to optimize therapeutic efficacy while minimizing toxicity through the maintenance of steady-state plasma concentrations within the therapeutic range [40]. Studies have demonstrated that these systems offer multiple advantages, including improved patient compliance through reduced dosing frequency, minimized fluctuations in plasma drug levels, decreased incidence of adverse effects, and reduced total drug consumption over the treatment period [41]. The ideal sustained release system should provide predictable and reproducible release characteristics, independent of physiological and environmental factors encountered in the gastrointestinal tract [42].

3.2.2 Classification of Sustained Release Systems

The scientific literature describes various classification schemes for sustained release systems based on their release mechanisms and structural characteristics [43]. Diffusion-controlled systems rely on the diffusion of drug molecules through a rate-controlling polymer membrane or matrix, with release kinetics governed by Fick's laws of diffusion [44]. These systems can be further subdivided into reservoir devices, where the drug core is surrounded by a polymeric membrane, and matrix devices, where the drug is uniformly

dispersed throughout a polymeric carrier [45].

Dissolution-controlled systems achieve sustained release through slow dissolution of drug particles or through gradual erosion of a polymer matrix [46]. Research has shown that these systems can be designed using poorly soluble drug derivatives, coating drug particles with slowly dissolving materials, or incorporating drugs into slowly eroding polymeric matrices [47]. Osmotically controlled systems utilize osmotic pressure as the driving force for drug release, with water entering the system through a semipermeable membrane and forcing the drug solution out through a laser-drilled orifice [48].

AIM AND OBJECTIVES

4.1 Aim of the Study

The primary aim of the present investigation is to develop and comprehensively evaluate sustained release tablets of naproxen sodium 500mg using hydrophilic polymer-based matrix technology. This research endeavors to formulate tablets that provide controlled and prolonged drug release over an extended period, typically 12 to 24 hours, thereby reducing the dosing frequency from conventional two to three times daily administration to once or twice daily dosing. The development of such a formulation is expected to enhance patient compliance, minimize fluctuations in plasma drug concentrations, reduce the incidence of adverse effects associated with peak plasma levels, and improve overall therapeutic outcomes in patients requiring long-term naproxen therapy for chronic inflammatory and pain conditions.

The study aims to employ a systematic, scientifically rigorous approach to formulation development, incorporating contemporary pharmaceutical development principles including Quality by Design concepts where appropriate. By investigating various formulation parameters and their effects on drug release characteristics, this research seeks to identify optimal formulation compositions that deliver consistent, predictable, and therapeutically appropriate drug release profiles. Furthermore, the study aims to establish the stability characteristics of the developed formulations, ensuring that the sustained release properties remain consistent throughout the proposed shelf-life of the product.

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4.2 Specific Objectives

To accomplish the stated aim, the following specific objectives have been established for this research work.

4.2.1 Preformulation Studies

To conduct comprehensive preformulation characterization of naproxen sodium and selected pharmaceutical excipients, including evaluation of physicochemical properties such as melting point, solubility in various media, particle size distribution, and bulk flow properties. These studies will establish a foundation for rational formulation development and provide baseline data for subsequent formulation work. To perform drug-excipient compatibility studies using appropriate analytical techniques such as Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) to identify any potential interactions between naproxen sodium and proposed excipients. These compatibility assessments will ensure the selection of excipients that do not adversely affect drug stability or performance.

4.2.2 Formulation Development

To design and prepare multiple formulations of naproxen sodium sustained release tablets using various types and concentrations of hydrophilic polymers, particularly hydroxypropyl methylcellulose (HPMC) of different viscosity grades. The formulation design will systematically vary polymer type, polymer concentration, and other relevant formulation parameters to understand their individual and interactive effects on tablet properties and drug release characteristics.

To optimize the composition of excipients including diluents, lubricants, and glidants to achieve tablets with acceptable physical and mechanical properties while maintaining desired drug release characteristics. This optimization will ensure that the final formulation is both therapeutically effective and manufacturable using conventional pharmaceutical equipment and processes.

To employ appropriate powder blending and direct compression techniques to manufacture tablets with uniform drug content, consistent weight, adequate mechanical strength, and reproducible release properties. The manufacturing process will be designed to be scalable and transferable to commercial production settings.

PLAN OF WORK

5.1 Overview of Research Methodology

The research work will be executed in a systematic and sequential manner, following a logical progression from initial material characterization through formulation development, evaluation, optimization, and stability assessment. The entire study will be conducted in compliance with good laboratory practices and pharmaceutical quality standards to ensure the reliability and reproducibility of results.

6.1 Results and Discussion

6.1.1 Preformulation Studies

Organoleptic Properties: Naproxen sodium appeared as a white to off-white crystalline powder with a characteristic odor and bitter taste. The powder showed good flow properties when visually observed.

Melting Point: The melting point of naproxen sodium was found to be 256°C, which is in accordance with the reported literature value (255-257°C), indicating the purity of the drug sample.

Solubility Studies: The solubility of naproxen sodium in various media is presented in Table 6.2.

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Table 6.2: Solubility of Naproxen Sodium in Different Media

Medium	**Solubility (mg/mL)**	**Classification**
Distilled Water	28.5 ± 1.2	Freely soluble
0.1N HCl (pH 1.2)	3.8 ± 0.4	Slightly soluble
Phosphate Buffer pH 6.8	42.3 ± 1.8	Freely soluble
Phosphate Buffer pH 7.4	48.6 ± 2.1	Freely soluble

(Values represent mean ± SD, n=3)

Naproxen sodium demonstrated pH-dependent solubility, being less soluble in acidic medium (pH 1.2) and showing significantly higher solubility in neutral to slightly alkaline pH. This behavior is attributed to the weakly acidic nature of naproxen (pKa 4.2), which exists predominantly in the ionized form at higher pH values, enhancing its aqueous solubility. The high solubility at pH 7.4 confirmed the suitability of phosphate buffer pH 7.4 as the dissolution medium for in vitro dissolution studies.

UV Spectroscopic Analysis: The UV spectrum of naproxen sodium in phosphate buffer pH 7.4 showed maximum absorption (λmax) at 271 nm. This wavelength was selected for all subsequent spectrophotometric analyses.

Calibration Curve: The calibration curve of naproxen sodium in phosphate buffer pH 7.4 demonstrated excellent linearity in the concentration range of 2-20 µg/mL. The regression equation was: $y = 0.0547x + 0.0021$ ($R^2 = 0.9998$) where y = absorbance and x = concentration (µg/mL)

The high correlation coefficient ($R^2 = 0.9998$) indicated good linearity and compliance with Beer- Lambert's law in the studied concentration range.

Particle Size Analysis: The particle size distribution of naproxen sodium is presented in Table 6.3.

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Table 6.3: Particle Size Distribution of Naproxen Sodium

Sieve Number (Mesh)	Particle Size Range (µm)	Weight Retained (g)	Percentage Retained (%)	Cumulative % Retained
20	>850	2.4	2.4	2.4
40	425-850	28.6	28.6	31.0
60	250-425	45.8	45.8	76.8
80	180-250	18.2	18.2	95.0
100	150-180	3.5	3.5	98.5
Pan	<150	1.5	1.5	100.0

The majority of naproxen sodium particles (45.8%) were in the size range of 250-425 µm, with cumulative 76.8% of particles below 425 µm. This particle size distribution was considered suitable for tablet formulation.

6.1.2 Kinetic Analysis of Drug Release

The dissolution data were fitted to various kinetic models and the correlation coefficients (R^2) were calculated to determine the best-fit model. The kinetic parameters for selected formulations are presented in Table 6.8.

Table 6.8: Kinetic Parameters of Drug Release from Selected Formulations

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Formulation	Zero-Order (R^2)	First-Order (R^2)	Higuchi (R^2)	Korsmeyer-Peppas (R^2)	n value	Hixson-Crowell (R^2)	Best Fit Model
F3	0.9845	0.9654	0.9912	0.9923	0.6124	0.9723	Korsmeyer-Peppas
F6	0.9912	0.9702	0.9945	0.9958	0.5842	0.9768	Korsmeyer-Peppas
F8	0.9886	0.9687	0.9934	0.9951	0.5673	0.9745	Korsmeyer-Peppas
F9	0.9823	0.9621	0.9898	0.9916	0.5521	0.9698	Korsmeyer-Peppas
F12	0.9924	0.9715	0.9952	0.9968	0.6285	0.9782	Korsmeyer-Peppas

Discussion of Kinetic Analysis:

All selected formulations showed good correlation with the Korsmeyer-Peppas model, with R^2 values exceeding 0.99, indicating this model best described the drug release mechanism. The release exponent (n) values ranged from 0.5521 to 0.6285, falling between 0.5 and 1.0, which indicates anomalous (non-Fickian) transport. This suggests that drug release from the matrix tablets is controlled by a combination of drug diffusion through the swollen polymer matrix and polymer chain relaxation/erosion.

Formulations also showed high correlation with the Higuchi model ($R^2 > 0.98$), which is characteristic of diffusion-controlled release from matrix systems. The good fit with zero-order kinetics, particularly for F6 and F12 ($R^2 > 0.99$), indicates that these formulations achieved relatively constant release rates over time, which is desirable for sustained release formulations.

CONCLUSION

The present investigation successfully developed and evaluated sustained release tablets of naproxen sodium 500mg using hydrophilic matrix technology. The research was conducted systematically, progressing through preformulation characterization, formulation design and development, comprehensive physicochemical evaluation, dissolution studies, kinetic analysis, and stability assessment.

Preformulation studies established the physicochemical properties of naproxen sodium, including melting point (256°C), pH-dependent solubility (highest at pH 7.4), and UV absorption maximum (271 nm). Drug-excipient compatibility studies using FTIR and DSC confirmed the absence of interactions between naproxen sodium and the selected excipients. Flow property evaluations demonstrated that all powder blends possessed good to excellent flow characteristics suitable for direct compression.

Twelve formulations were designed and prepared using different types and concentrations of polymers, including HPMC K4M, HPMC K15M, HPMC K100M, and combinations of HPMC K4M with Carbopol 934P. All formulations were manufactured by direct compression method and evaluated for physical parameters including weight variation, hardness, friability, thickness, diameter, and drug content uniformity. All formulations met pharmacopeial requirements for these parameters.

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