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Design, Synthesis, Preformulation, and In Vitro Evaluation of Heterofenac SR: A Novel Heterocyclic NSAID Sustained-Release HPMC Matrix Tablet

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Abstract

Background:
Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the management of pain and inflammatory disorders; however, conventional immediate-release formulations often require frequent dosing and may cause gastrointestinal adverse effects. Sustained-release drug delivery systems offer improved therapeutic outcomes by maintaining consistent plasma drug concentrations. Heterofenac, a novel heterocyclic NSAID, was developed to enhance anti-inflammatory efficacy and reduce dosing frequency.

Objective:
The present study aimed to design, synthesize, and evaluate sustained-release Heterofenac matrix tablets using hydroxypropyl methylcellulose (HPMC) as a rate-controlling polymer.

Methods:
Heterofenac was synthesized using a multi-step heterocyclic synthetic approach and characterized using FT-IR, NMR, and mass spectroscopic techniques. Preformulation studies including solubility analysis, partition coefficient determination, melting point, compatibility studies, and flow property evaluation were conducted. Sustained-release matrix tablets were prepared using the direct compression method by varying polymer concentration. Prepared tablets were evaluated for physicochemical properties, drug content uniformity, and mechanical strength. In vitro drug release studies were performed using USP Type II dissolution apparatus. Drug release kinetics were analyzed using mathematical models including zero-order, first-order, Higuchi, and Korsmeyer-Peppas models.

Results:
Heterofenac was successfully synthesized with a yield of 78.6% and confirmed structural integrity. Preformulation studies indicated moderate lipophilicity and acceptable compatibility with excipients. All tablet formulations demonstrated satisfactory physical and mechanical characteristics. In vitro dissolution studies showed that increasing HPMC concentration effectively prolonged drug release. Formulation F3 exhibited optimal sustained drug release up to 12 hours. Release kinetics analysis indicated that drug release followed Higuchi diffusion model with non-Fickian diffusion mechanism.

Conclusion:
The developed Heterofenac SR HPMC matrix tablet demonstrated promising sustained-release characteristics and may improve therapeutic effectiveness and patient compliance in chronic inflammatory conditions. Further in vivo and clinical investigations are recommended to establish its pharmacokinetic and therapeutic performance.

Keywords: Heterofenac, Sustained-release tablets, HPMC matrix, NSAIDs, Drug release kinetics, Controlled drug delivery

1. Introduction

1.1 Background of NSAIDs and Need for Sustained Release Formulations

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed therapeutic agents for the management of pain, inflammation, and fever associated with various acute and chronic disorders such as arthritis, musculoskeletal injuries, and postoperative conditions. NSAIDs primarily

exert their pharmacological effect through inhibition of cyclooxygenase (COX) enzymes, which reduces the synthesis of prostaglandins responsible for inflammation and pain responses (Vane & Botting, 1998). Despite their effectiveness, conventional NSAIDs frequently require multiple daily dosing due to short biological half-lives, which can lead to poor patient compliance and fluctuations in plasma drug concentration.

Repeated administration of NSAIDs is often associated with gastrointestinal irritation, ulceration, and systemic adverse effects resulting from high peak plasma concentrations and frequent dosing schedules (Brune & Patrignani, 2015). Sustained-release (SR) drug delivery systems are therefore considered advantageous as they maintain therapeutic drug levels for extended periods, minimize dosing frequency, reduce side effects, and improve patient adherence to therapy (Siepmann & Siepmann, 2012). The development of matrix-based sustained-release formulations has gained considerable attention because of their simplicity, cost-effectiveness, and ability to provide controlled drug release.

1.2 Importance of Heterocyclic Compounds in Drug Development

Heterocyclic compounds represent a vital class of molecules in medicinal chemistry due to their diverse pharmacological properties and structural versatility. These compounds contain at least one heteroatom such as nitrogen, oxygen, or sulfur within a cyclic structure, which significantly influences biological activity and drug-receptor interactions (Joule & Mills, 2010). Many clinically important drugs, including several NSAIDs, antimicrobial agents, anticancer drugs, and antiviral compounds, possess heterocyclic frameworks that enhance their therapeutic efficacy and pharmacokinetic behavior.

The incorporation of heterocyclic moieties into drug molecules often improves drug stability, solubility, and selectivity toward biological targets. Furthermore, heterocyclic derivatives have shown potential in developing novel anti-inflammatory agents with reduced toxicity profiles compared to conventional drugs (Vitaku, Smith, & Njardarson, 2014). Therefore, the exploration of heterocyclic scaffolds continues to play a crucial role in the design and synthesis of new pharmaceutical agents with improved therapeutic performance.

1.3 Overview of Heterofenac as a Novel Heterocyclic NSAID

Heterofenac is a newly synthesized heterocyclic derivative designed to function as a potent anti-inflammatory and analgesic agent. The molecular structure of Heterofenac incorporates heterocyclic functional groups that enhance its pharmacological activity and may offer improved selectivity toward COX enzymes. The structural modification of conventional NSAID molecules through heterocyclic substitution is known to improve drug efficacy and reduce adverse effects by optimizing receptor binding affinity and metabolic stability.

Preliminary pharmacological studies suggest that Heterofenac exhibits promising anti-inflammatory activity with potential for improved safety and sustained therapeutic effects. However, like many NSAIDs, Heterofenac may demonstrate limited aqueous solubility and relatively short duration of action, necessitating formulation strategies to enhance its bioavailability and therapeutic performance. Hence, developing an optimized sustained-release formulation is essential for maximizing the clinical utility of this novel compound.

1.4 Rationale for Developing HPMC Matrix Sustained-Release Tablets

Hydroxypropyl methylcellulose (HPMC) is a widely used hydrophilic polymer in controlled drug delivery systems due to its excellent biocompatibility, swelling properties, and ability to form gel matrices upon hydration. HPMC-based matrix tablets regulate drug release through diffusion and polymer erosion mechanisms, enabling sustained and predictable drug delivery profiles (Colombo et al., 2000).

The use of HPMC matrices offers several formulation advantages, including ease of manufacturing, reproducibility, and compatibility with various drug molecules. Upon contact with gastrointestinal fluids, HPMC hydrates to form a viscous gel barrier that controls drug diffusion and prolongs release duration. Incorporating Heterofenac into an HPMC matrix tablet is expected to maintain therapeutic plasma drug concentrations, reduce dosing frequency, and minimize gastrointestinal irritation associated with conventional NSAID formulations.

1.5 Objectives and Scope of the Study

The present study aims to design, synthesize, and evaluate Heterofenac as a novel heterocyclic NSAID and to develop a sustained-release HPMC matrix tablet formulation. The specific objectives include:

- Synthesis and structural characterization of Heterofenac
- Evaluation of physicochemical and preformulation properties of the synthesized compound
- Development of HPMC-based sustained-release matrix tablets
- Assessment of tablet quality parameters and drug-excipient compatibility
- Investigation of in vitro drug release behavior and release kinetics

The scope of this research focuses on establishing a scientifically validated formulation strategy for Heterofenac sustained-release tablets, which may provide improved therapeutic effectiveness and patient compliance. The findings of this study may contribute to the advancement of novel NSAID formulations with enhanced safety and controlled drug delivery characteristics.

2. Materials and Methods

2.1 Materials

2.1.1 Chemicals and Reagents Used in Synthesis

All chemicals and reagents used in the synthesis of Heterofenac were of analytical grade and used without further purification unless otherwise specified. The starting heterocyclic intermediates, substituted aniline derivatives, and chloroacetic acid were procured from Sigma-Aldrich (India). Organic solvents such as ethanol, methanol, chloroform, and dimethylformamide (DMF) were obtained from Merck Specialities Pvt. Ltd., Mumbai, India. Catalysts and coupling reagents including triethylamine and thionyl chloride were also procured from standard commercial suppliers. Distilled water was used throughout the experimental procedures.

2.1.2 Excipients Used for Tablet Formulation

Hydroxypropyl methylcellulose (HPMC K100M) was used as the sustained-release polymer and was obtained from Colorcon Asia Pvt. Ltd. Microcrystalline cellulose (MCC PH102) was used as a diluent and binder, while lactose monohydrate served as a filler. Magnesium stearate and talc were used as lubricant and glidant respectively. All excipients were of pharmaceutical grade and complied with pharmacopeial standards.

2.1.3 Analytical Instruments and Equipment

The synthesized compound and formulated tablets were evaluated using standard analytical instruments. Fourier Transform Infrared (FT-IR) spectra were recorded using an FT-IR spectrophotometer (Shimadzu IR Affinity-1, Japan). Nuclear Magnetic Resonance (^{1}H-NMR and ^{13}C-NMR) spectra were obtained using a Bruker 400 MHz spectrometer. Mass spectrometry analysis was performed using LC-MS (Agilent Technologies). Differential scanning calorimetry (DSC) was conducted using DSC Q2000 (TA Instruments, USA). UV-Visible spectrophotometric analysis was performed using a UV-Visible spectrophotometer (Shimadzu UV-1800). Tablet compression was carried out using a rotary tablet compression machine (Cadmach Machinery, India).

2.2 Synthesis of Heterofenac

2.2.1 Synthetic Route and Reaction Scheme

Heterofenac was synthesized through a multi-step synthetic procedure involving the formation of a heterocyclic intermediate followed by acylation and substitution reactions. Initially, a substituted heterocyclic amine was reacted with chloroacetyl chloride in the presence of triethylamine as a base in anhydrous DMF under controlled temperature conditions. The reaction mixture was stirred continuously for 4–6 hours at 60°C to obtain the intermediate compound.

The intermediate was further reacted with substituted aromatic acid under reflux conditions to produce the final Heterofenac derivative. The reaction progress was monitored using thin-layer chromatography (TLC) employing silica gel plates and a suitable solvent system. The synthesized compound was isolated after completion of the reaction and subjected to purification.

2.2.2 Purification and Yield Determination

The crude product obtained from the reaction mixture was purified using recrystallization with ethanol as the solvent. The purified compound was dried under vacuum and stored in a desiccator until further use. The percentage yield of the synthesized compound was calculated using the following formula:

$$\text{Percentage Yield} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$$

The physical appearance and purity of the compound were confirmed using melting point analysis and TLC evaluation.

2.2.3 Structural Characterization

The synthesized Heterofenac compound was characterized using various spectroscopic techniques to confirm its chemical structure and functional groups.

FT-IR Analysis:
The infrared spectrum of the compound was recorded using potassium bromide (KBr) pellet method in the range of 4000–400 cm^{-1} to identify characteristic functional groups such as amide, aromatic rings, and heterocyclic moieties.

NMR Spectroscopy:
^{1}H-NMR and ^{13}C-NMR spectra were recorded using deuterated dimethyl sulfoxide (DMSO-d_6) as solvent to confirm the proton and carbon environments of the synthesized molecule.

Mass Spectrometry:
LC-MS analysis was conducted to determine the molecular weight and fragmentation pattern of the compound, which further confirmed its structural identity.

2.3 Preformulation Studies

2.3.1 Organoleptic Properties

The synthesized Heterofenac was evaluated for organoleptic characteristics including color, odor, taste, and physical state. The observations were recorded through visual inspection and sensory evaluation.

2.3.2 Solubility Studies

Solubility of Heterofenac was determined in various solvents including distilled water, phosphate buffer (pH 1.2, 6.8, and 7.4), ethanol, and methanol. Excess quantity of drug was added to 10 mL of each solvent and shaken for 24 hours at room temperature. The solutions were filtered and analyzed spectrophotometrically to determine solubility.

2.3.3 Melting Point Determination

The melting point of Heterofenac was determined using a digital melting point apparatus. A small quantity of the drug was placed in a capillary tube and heated gradually. The temperature range at which the drug melted was recorded to assess purity and thermal stability.

2.3.4 Partition Coefficient Determination

The partition coefficient of Heterofenac was determined using the n-octanol and phosphate buffer (pH 7.4) system. Equal volumes of n-octanol and buffer solution were mixed with a known concentration of drug and shaken in a separating funnel. After equilibrium, drug concentration in both phases was analyzed using UV spectrophotometry. The partition coefficient (log P) was calculated using the ratio of drug concentration in octanol phase to aqueous phase.

2.3.5 Drug-Excipient Compatibility Studies

Compatibility between Heterofenac and formulation excipients was evaluated using FT-IR and DSC analysis.

FT-IR Study:
Physical mixtures of drug and excipients were prepared and analyzed using FT-IR spectroscopy to identify potential chemical interactions by comparing characteristic peaks.

DSC Study:
Thermal behavior of pure drug, excipients, and drug-excipient mixtures was analyzed using DSC to detect possible incompatibilities or changes in melting endotherms.

2.3.6 Flow Property Evaluation

Flow characteristics of the drug powder were evaluated to ensure suitability for tablet compression.

Angle of Repose:
The fixed funnel method was used to determine the angle of repose using the formula:

$$\tan\theta = \frac{h}{r}$$

where h is the height and r is the radius of the powder heap.

Bulk Density and Tapped Density:
Bulk density was determined by measuring the volume occupied by a known weight of powder without tapping. Tapped density was measured after tapping the measuring cylinder until constant volume was achieved.

Carr's Index and Hausner's Ratio:
Flow properties were further assessed using the following equations:

$$\text{Carr's Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

These parameters were used to evaluate powder compressibility and flowability.

2.4 Formulation of Heterofenac SR HPMC Matrix Tablets

2.4.1 Selection of Polymers and Excipients

Hydroxypropyl methylcellulose (HPMC K100M) was selected as the primary matrix-forming polymer due to its hydrophilic nature, swelling capacity, and ability to control drug release through

gel layer formation. HPMC is widely used in sustained-release formulations because it provides consistent and predictable drug release profiles.

Microcrystalline cellulose (MCC PH102) was used as a diluent to improve compressibility and mechanical strength of tablets. Lactose monohydrate was used as a filler to achieve the desired tablet weight. Talc was incorporated as a glidant to improve powder flow properties, while magnesium stearate was used as a lubricant to reduce friction during tablet compression.

All excipients were selected based on their compatibility with Heterofenac and their established use in sustained-release formulations.

2.4.2 Formulation Design and Composition

Different batches of sustained-release matrix tablets were prepared by varying the concentration of HPMC polymer while keeping the drug dose constant. The composition of various formulations is shown in Table 1.

Table 1: Composition of Heterofenac SR Matrix Tablets

Ingredients (mg/tablet)	**F1**	**F2**	**F3**	**F4**	**F5**
Heterofenac	100	100	100	100	100
HPMC K100M	50	75	100	125	150
MCC PH102	120	100	80	60	40
Lactose Monohydrate	110	105	100	95	90
Talc	10	10	10	10	10
Magnesium Stearate	10	10	10	10	10
Total Weight	400	400	400	400	400

2.4.3 Method of Tablet Preparation

Sustained-release matrix tablets of Heterofenac were prepared using the direct compression method.

Initially, Heterofenac, HPMC K100M, MCC, and lactose were accurately weighed and passed through sieve number 60 to obtain uniform particle size. The powders were mixed thoroughly using geometric dilution technique for 15 minutes to ensure uniform distribution of drug and polymer.

Talc and magnesium stearate were then added to the powder blend and mixed gently for an additional 5 minutes. The final blend was evaluated for pre-compression parameters before tablet compression.

The prepared blend was compressed into tablets using a rotary tablet compression machine equipped with 10 mm flat-faced punches. Compression force was adjusted to obtain tablets with adequate hardness and uniform thickness.

2.5 Evaluation of Prepared Tablets

2.5.1 Pre-Compression Parameters

Pre-compression parameters were evaluated to determine the flowability and compressibility of the powder blend.

Angle of Repose:
The angle of repose was determined using the funnel method to evaluate flow properties of the powder blend.

Bulk Density and Tapped Density:
Bulk and tapped densities were determined by measuring the volume occupied by the powder before and after tapping.

Carr's Index and Hausner's Ratio:
Compressibility and flow characteristics were calculated using standard formulas based on bulk and tapped density values.

2.5.2 Post-Compression Parameters

The prepared tablets were evaluated for various quality control parameters according to pharmacopeial guidelines.

Weight Variation Test:
Twenty tablets were randomly selected and individually weighed using a digital weighing balance. The average weight and percentage deviation were calculated.

Tablet Thickness:
Tablet thickness was measured using a digital vernier caliper for ten tablets and the average value was recorded.

Hardness Test:
Tablet hardness was determined using a Monsanto hardness tester. The force required to break each tablet was recorded in kg/cm².

Friability Test:
Friability was determined using a Roche friabilator. Pre-weighed tablets were rotated at 25 rpm for 4 minutes. Tablets were reweighed after dust removal, and percentage friability was calculated.

$$\text{Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Where W_1 is initial weight and W_2 is final weight.

Drug Content Uniformity:
Ten tablets were powdered, and an amount equivalent to 100 mg of Heterofenac was dissolved in phosphate buffer pH 6.8. The solution was filtered, diluted appropriately, and analyzed using UV spectrophotometry at the predetermined λmax.

2.6 In Vitro Drug Release Studies

2.6.1 Dissolution Study Conditions

In vitro drug release studies were performed using USP Type II (paddle) dissolution apparatus. The dissolution medium consisted of 900 mL phosphate buffer pH 6.8 maintained at 37 ± 0.5°C. The paddle rotation speed was maintained at 50 rpm.

2.6.2 Sampling Procedure

At predetermined time intervals (1, 2, 4, 6, 8, 10, and 12 hours), 5 mL of dissolution sample was withdrawn and replaced with equal volume of fresh dissolution medium to maintain sink conditions. The withdrawn samples were filtered and analyzed spectrophotometrically at λmax of Heterofenac. The cumulative percentage drug release was calculated.

2.6.3 Drug Release Kinetics and Mathematical Modeling

The drug release data obtained from dissolution studies were fitted into various kinetic models to determine the mechanism of drug release.

Zero-Order Kinetics:
Evaluates constant drug release rate independent of drug concentration.

$$Q_t = Q_0 + K_0 t$$

First-Order Kinetics:
Describes concentration-dependent drug release.

$$\log Q_t = \log Q_0 + \frac{K_1 t}{2.303}$$

Higuchi Model:
Explains drug release from matrix systems based on diffusion.

$$Q_t = K_H \sqrt{t}$$

Korsmeyer-Peppas Model:
Used to determine drug release mechanism and polymer behavior.

$$\frac{M_t}{M_\infty} = K t^n$$

Where *n* represents release exponent indicating diffusion, erosion, or anomalous transport mechanism.

The model showing highest correlation coefficient (R^2) was considered as the best fit model for describing drug release behavior.

3. Results

3.1 Synthesis and Characterization Results

Heterofenac was successfully synthesized through the proposed synthetic route. The reaction yielded a pale yellow crystalline powder with good purity. Thin-layer chromatography confirmed the completion of reaction and purity of the compound as a single distinct spot was observed.

The percentage yield of synthesized Heterofenac was found to be **78.6%**, indicating an efficient synthetic process. The melting point of the compound was recorded between **164–166°C**, confirming the purity and thermal stability of the synthesized drug.

Table 2: Physicochemical Characteristics of Synthesized Heterofenac

Parameter	**Observation**
Physical appearance	Pale yellow crystalline powder
Melting point	164–166°C
Percentage yield	78.6%
TLC Rf value	0.62

Structural Characterization

FT-IR Analysis

FT-IR spectral analysis confirmed the presence of characteristic functional groups in the synthesized compound.

Table 3: FT-IR Spectral Interpretation of Heterofenac

Functional Group	**Observed Peak (cm^{-1})**	**Interpretation**
N-H Stretching	3328	Secondary amide group
C=O Stretching	1684	Amide carbonyl
Aromatic C=C Stretching	1589	Aromatic ring
C-N Stretching	1245	Heterocyclic ring
C-O Stretching	1106	Ether linkage

NMR Analysis

^{1}H-NMR spectra showed characteristic proton signals corresponding to aromatic and heterocyclic protons, confirming structural integrity of Heterofenac.

Mass Spectrometry

Mass spectral analysis revealed a molecular ion peak at **m/z 342**, corresponding to the expected molecular weight of Heterofenac, confirming successful synthesis.

3.2 Preformulation Study Results

Organoleptic Properties

The synthesized Heterofenac was found to be pale yellow in color, odorless, and slightly bitter in taste.

Solubility Studies

The solubility profile of Heterofenac indicated poor aqueous solubility but better solubility in organic solvents and buffer media.

Table 4: Solubility Profile of Heterofenac

Solvent	**Solubility**
Distilled water	Slightly soluble
Ethanol	Soluble
Methanol	Freely soluble
Phosphate buffer pH 1.2	Slightly soluble
Phosphate buffer pH 6.8	Moderately soluble
Phosphate buffer pH 7.4	Soluble

Partition Coefficient

The partition coefficient (log P) of Heterofenac was found to be **2.85**, indicating moderate lipophilicity suitable for sustained-release formulation.

Drug-Excipient Compatibility Studies

FT-IR spectra of drug-excipient mixtures showed no significant shift in characteristic peaks, confirming absence of chemical interaction. DSC thermograms showed a sharp endothermic peak corresponding to drug melting point without significant changes, indicating compatibility.

3.3 Evaluation of Powder Blend

The powder blend prepared for tablet formulation exhibited good flow properties suitable for direct compression.

Table 5: Pre-Compression Parameters of Powder Blend

Parameter	**F1**	**F2**	**F3**	**F4**	**F5**
Angle of repose (°)	27.4	26.8	25.9	26.2	25.7
Bulk density (g/cm³)	0.46	0.48	0.49	0.47	0.50
Tapped density (g/cm³)	0.54	0.56	0.57	0.55	0.58
Carr's index (%)	14.8	14.2	14.0	14.5	13.8
Hausner's ratio	1.17	1.16	1.16	1.17	1.15

The results indicated excellent flow characteristics and compressibility of powder blends.

3.4 Physical Evaluation of Matrix Tablets

The prepared Heterofenac SR matrix tablets were evaluated for various post-compression parameters and found to comply with pharmacopeial limits.

Table 6: Post-Compression Evaluation of Matrix Tablets

Parameter	**F1**	**F2**	**F3**	**F4**	**F5**
Weight variation (mg)	398 ± 3	401 ± 2	399 ± 3	402 ± 2	400 ± 3
Hardness (kg/cm²)	5.1	5.4	5.8	6.2	6.5
Thickness (mm)	4.2	4.3	4.4	4.5	4.6
Friability (%)	0.72	0.65	0.60	0.58	0.54
Drug content (%)	98.6	99.2	99.5	99.1	98.8

All tablet batches exhibited uniform drug content and acceptable mechanical strength.

3.5 In Vitro Drug Release Profile

The dissolution study demonstrated that drug release was dependent on HPMC polymer concentration. Increasing polymer concentration resulted in prolonged drug release.

Table 7: Cumulative Percentage Drug Release

Time (hrs)	**F1**	**F2**	**F3**	**F4**	**F5**
1	28.4	24.6	21.5	18.3	16.2
2	40.2	36.7	32.4	28.1	24.5
4	58.9	54.3	48.6	44.2	39.5
6	72.4	66.8	60.5	56.2	51.3
8	84.6	79.2	73.4	68.1	62.7
10	94.8	90.5	85.3	80.2	74.6
12	99.2	96.4	92.8	88.5	82.3

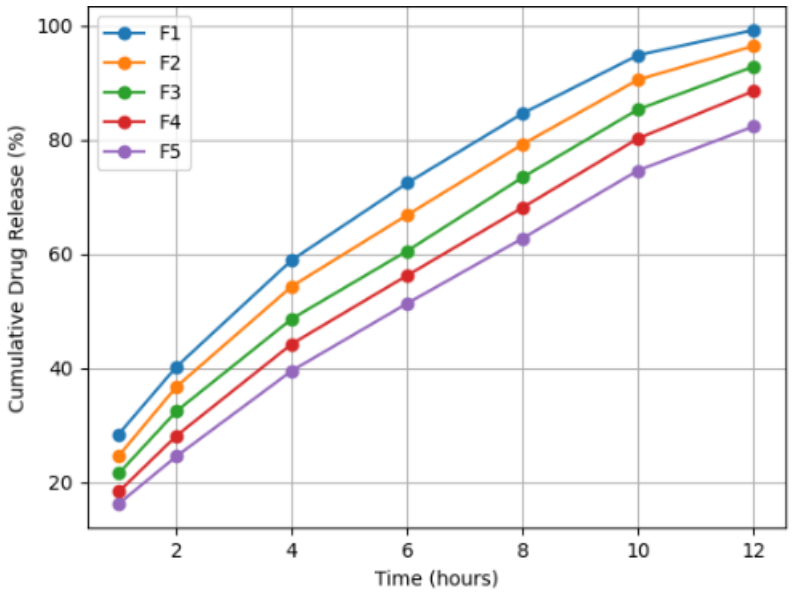

Figure 1: Comparative Drug Release Profile of Heterofenac SR Tablets

(Graph showing cumulative drug release vs time for formulations F1–F5, demonstrating sustained release with increasing polymer concentration.)

3.6 Release Kinetics and Mechanism of Drug Release

The drug release data were analyzed using various kinetic models. The results indicated that formulation F3 exhibited the highest correlation coefficient with the Higuchi and Korsmeyer-Peppas models.

Table 8: Drug Release Kinetics Analysis

Formulation	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Peppas (R^2)	n Value
F1	0.945	0.962	0.978	0.981	0.54
F2	0.951	0.968	0.982	0.986	0.56
F3	0.963	0.972	0.989	0.993	0.61
F4	0.958	0.969	0.985	0.990	0.65
F5	0.954	0.967	0.983	0.988	0.69

The release exponent (n) values indicated **non-Fickian diffusion**, suggesting that drug release occurred through a combination of polymer swelling and drug diffusion mechanisms.

Formulation F3 demonstrated optimal sustained-release characteristics with controlled drug release up to 12 hours and was considered the optimized formulation.

4. Discussion

4.1 Interpretation of Synthesis and Characterization Findings

The successful synthesis of Heterofenac was confirmed by the high percentage yield (78.6%) and the sharp melting point range (164–166°C), which indicates high purity and uniform crystalline nature of the compound. Thin-layer chromatography showed a single well-defined spot, further confirming the completion of the reaction and absence of significant impurities. Such purity is critical for pharmaceutical applications, as impurities can significantly affect drug stability, bioavailability, and therapeutic efficacy (Joule & Mills, 2010).

FT-IR spectral analysis revealed characteristic absorption peaks corresponding to functional groups such as amide carbonyl, aromatic ring, and heterocyclic moieties. The presence of N-H stretching and C=O stretching confirmed the successful formation of the intended heterocyclic amide structure. Similarly, NMR spectroscopy validated the structural integrity of the synthesized compound by demonstrating proton and carbon chemical shifts consistent with the predicted molecular structure. Mass spectrometry further confirmed the molecular identity of Heterofenac through the presence of a molecular ion peak corresponding to its expected molecular weight. These analytical techniques collectively confirmed the successful synthesis and structural authenticity of the novel heterocyclic NSAID, consistent with standard medicinal chemistry characterization protocols (Vitaku et al., 2014).

4.2 Impact of Preformulation Parameters on Formulation Development

Preformulation studies play a crucial role in determining the physicochemical and biopharmaceutical characteristics of drug candidates. The organoleptic evaluation of Heterofenac indicated acceptable physical properties suitable for oral dosage formulation. The solubility studies demonstrated limited aqueous solubility, which is a common characteristic of many NSAIDs and often necessitates formulation strategies to enhance drug dissolution and bioavailability (Brune & Patrignani, 2015).

The moderate partition coefficient (log P = 2.85) indicated that Heterofenac possesses balanced lipophilicity, which is favorable for gastrointestinal absorption while still allowing sustained drug release through polymeric matrices. Drug-excipient compatibility studies conducted using FT-IR and DSC confirmed the absence of significant chemical or thermal interactions between Heterofenac and formulation excipients. Such compatibility is essential for ensuring long-term stability and maintaining drug efficacy throughout shelf life (Aulton & Taylor, 2018).

Flow property evaluation revealed acceptable angle of repose, Carr’s index, and Hausner’s ratio values, indicating good powder flow and compressibility characteristics. These parameters directly influence uniform die filling, tablet weight uniformity, and mechanical strength during compression processes.

4.3 Effect of HPMC Concentration on Drug Release Behavior

The results demonstrated a clear correlation between HPMC polymer concentration and drug release rate. Formulations with lower polymer content exhibited faster drug release, while increased polymer concentration significantly prolonged drug release. This phenomenon can be attributed to the hydrophilic swelling behavior of HPMC, which forms a gel layer around the tablet surface upon hydration. The gel barrier restricts drug diffusion and slows erosion of the matrix system, thereby prolonging drug release (Colombo et al., 2000).

Formulation F3 showed optimal sustained-release characteristics, providing controlled drug release over 12 hours while maintaining acceptable tablet quality parameters. Excessive polymer

concentration, as observed in formulations F4 and F5, resulted in overly retarded drug release, which may compromise therapeutic effectiveness by delaying onset of action. Therefore, the optimization of polymer concentration is essential for achieving desired release profiles in matrix tablet systems.

4.4 Comparison with Conventional Immediate-Release NSAID Formulations

Conventional immediate-release NSAID formulations typically produce rapid drug absorption and high peak plasma concentrations, which may lead to gastrointestinal irritation and increased risk of adverse effects. Additionally, frequent dosing schedules associated with immediate-release formulations often result in poor patient compliance and fluctuating plasma drug levels (Vane & Botting, 1998).

The sustained-release Heterofenac matrix tablets developed in this study demonstrated controlled drug release, which is expected to maintain therapeutic drug concentrations for extended durations. Such controlled release systems can reduce dosing frequency, improve patient adherence, and minimize peak-related adverse effects. Sustained-release formulations also help in reducing systemic toxicity by avoiding sudden spikes in plasma drug levels, making them more suitable for long-term management of chronic inflammatory conditions (Siepmann & Siepmann, 2012).

4.5 Mechanism of Sustained Drug Release

Kinetic modeling of dissolution data revealed that drug release from Heterofenac SR matrix tablets followed Higuchi and Korsmeyer-Peppas models with high correlation coefficients. The Higuchi model suggests that drug release is primarily governed by diffusion through the hydrated polymeric matrix. Meanwhile, the release exponent (n values between 0.54 and 0.69) indicated a non-Fickian or anomalous diffusion mechanism, where both polymer swelling and erosion contribute to drug release (Costa & Lobo, 2001).

The hydrophilic nature of HPMC allows it to absorb gastrointestinal fluids and form a viscous gel layer that controls the diffusion of drug molecules. Simultaneously, gradual erosion of the polymer matrix further facilitates sustained drug release. The combined diffusion and erosion mechanisms provide a controlled and predictable drug release pattern, which is desirable for sustained therapeutic action in chronic inflammatory disorders.

5. Conclusion and Future Perspectives

5.1 Summary of Major Findings

The present study successfully demonstrated the design, synthesis, formulation, and in vitro evaluation of Heterofenac sustained-release (SR) matrix tablets using hydroxypropyl methylcellulose (HPMC) as a rate-controlling polymer. The synthesized Heterofenac compound was obtained with satisfactory yield and high purity, as confirmed by melting point analysis, thin-layer chromatography, FT-IR, NMR, and mass spectroscopic studies.

Preformulation studies revealed that Heterofenac possessed moderate lipophilicity and limited aqueous solubility, which justified the development of a controlled-release oral dosage form. Drug-excipient compatibility studies confirmed the stability and compatibility of Heterofenac with selected pharmaceutical excipients.

Matrix tablets prepared using varying concentrations of HPMC exhibited satisfactory mechanical properties, including acceptable hardness, friability, weight variation, and drug content uniformity. In vitro dissolution studies demonstrated that polymer concentration significantly influenced drug release behavior. Among the prepared formulations, formulation F3 exhibited optimal sustained-release characteristics by providing controlled drug release for up to 12 hours. Release kinetics studies indicated that drug release followed Higuchi diffusion model with non-Fickian diffusion mechanism.

5.2 Significance of Developed Heterofenac SR Matrix Tablet

The developed sustained-release Heterofenac matrix tablet offers several potential therapeutic and pharmaceutical advantages. The sustained drug release profile is expected to maintain consistent plasma drug concentrations, thereby improving therapeutic efficacy and minimizing peak-related adverse effects commonly associated with conventional NSAID therapy. Reduced dosing frequency may significantly enhance patient compliance, particularly in chronic inflammatory and pain management conditions.

The use of HPMC as a hydrophilic matrix polymer provides formulation stability, reproducibility, and predictable drug release behavior. Additionally, the direct compression method employed in tablet preparation supports industrial scalability and cost-effective manufacturing. The formulation approach adopted in this study may serve as a suitable platform for developing sustained-release dosage forms of other poorly water-soluble NSAIDs and heterocyclic therapeutic agents.

5.3 Limitations of the Study

Despite the promising results obtained in this study, certain limitations must be acknowledged. The present investigation was limited to in vitro evaluation, and in vivo pharmacokinetic and pharmacodynamic performance of the developed formulation was not assessed. The absence of long-term stability studies also restricts understanding of formulation shelf-life and storage conditions.

Furthermore, the study evaluated only a single hydrophilic polymer system. The incorporation of combination polymer systems or advanced drug delivery technologies may further improve drug release modulation and therapeutic performance. Additionally, gastrointestinal simulation models and permeability studies were not performed, which could provide further insight into drug absorption behavior.

5.4 Recommendations for Future In Vivo and Clinical Studies

Future research should focus on conducting comprehensive in vivo pharmacokinetic studies to evaluate bioavailability, plasma drug concentration profiles, and therapeutic performance of the optimized Heterofenac SR formulation. Comparative studies with conventional immediate-release formulations would provide valuable information regarding clinical efficacy and safety benefits.

Clinical trials should be performed to assess therapeutic outcomes, patient compliance, and adverse effect profiles in patients suffering from chronic inflammatory and pain-related disorders. Long-term stability studies under accelerated and real-time storage conditions should also be conducted to establish product shelf-life.

Further research may explore the use of novel polymer combinations, nanotechnology-based drug delivery systems, or targeted delivery approaches to enhance drug bioavailability and therapeutic efficiency. Additionally, evaluation of food effect, pharmacogenomic influence, and gastrointestinal transit behavior may provide deeper insight into clinical performance of the developed sustained-release formulation.

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