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THERAPEUTIC ROLE OF NIMESULIDE IN ACUTE PAIN: FROM FORMULATION TO IN VIVO STUDY

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Abstract

Nimesulide, a selective cyclooxygenase-2 (COX-2) inhibitor, is a promising therapeutic agent for acute pain management owing to its rapid onset of action, favorable pharmacokinetics, and improved safety profile compared to conventional non-steroidal anti-inflammatory drugs (NSAIDs). The present study aimed to develop and evaluate Nimesulide tablets, focusing on their Preformulation, formulation, and pharmacological performance. Pre-compression and post-compression parameters confirmed acceptable flow and compressibility properties, with tablets demonstrating uniform weight, optimal hardness, low friability, and rapid disintegration. Drug content analysis revealed >98% uniformity, while in vitro release studies showed nearly complete drug release within 30 minutes, suggesting suitability for immediate pain relief. UV-spectrophotometric calibration confirmed linearity in the 6–28 µg/mL range ($R^2 > 0.99$). Solubility studies indicated poor aqueous solubility but better solubility in ethanol and acidic media. In vivo evaluation using the tail flick method in Wistar rats demonstrated a significant increase in pain threshold, with latency times increasing from 2 seconds (baseline) to 27 seconds at 1-hour post-administration, confirming a potent analgesic effect. Overall, the results validate Nimesulide's role as an effective and well-tolerated analgesic for acute pain management, supporting its clinical relevance in modern therapeutics.

Keywords: Nimesulide; Acute pain management; COX-2 inhibitor; Analgesic activity; Tablet formulation; In vitro drug release; Tail flick test; NSAIDs.

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INTRODUCTION

Acute pain, commonly arising from surgery, dental procedures, or musculoskeletal injuries, requires prompt and effective management to enhance recovery and patient comfort [1]. NSAIDs are widely used due to their analgesic and anti-inflammatory properties, but traditional non-selective agents often cause gastrointestinal and renal complications [2]. Nimesulide, a selective COX-2 inhibitor, offers a rapid onset of action, a short half-life, and strong plasma protein binding, making it effective for short-term pain relief [3]. Clinical studies have demonstrated its efficacy in dental pain, musculoskeletal injuries, and postoperative settings, with fewer gastrointestinal side effects compared to conventional NSAIDs [4]. Additionally, combining Nimesulide with paracetamol enhances analgesic outcomes without markedly increasing adverse effects [4]. With careful monitoring, particularly in patients with hepatic risk, Nimesulide remains a valuable option in acute pain management.

Materials and Methodology

Materials

Nimesulide (Active Pharmaceutical Ingredient, API) was procured from a certified supplier with purity >99%. The excipients employed were lactose, microcrystalline cellulose (MCC), starch, carboxymethyl cellulose (CMC), povidone K-30, magnesium stearate, and talc. All excipients were of analytical grade and used as received.

Chemicals used

The study was carried out using standard laboratory instruments, including a precision weighing balance, thermometer, hot plate, rotary tablet punching machine, friability tester, hardness tester, USP Type II dissolution apparatus, UV–Visible spectrophotometer, and Eddy's hot plate (analgesiometer). All instruments were calibrated before experimentation to ensure accuracy and reproducibility.

Preformulation Studies

Characterisation of Nimesulide

Organoleptic properties such as colour, odour, and taste were examined and recorded using standard descriptive terminology to confirm identity [5].

Solubility studies were conducted by adding an excess of drug to different solvents, including distilled water, 0.1 N HCl, glacial acetic acid, anhydrous ethanol, and ethyl acetate. The mixtures were agitated in a thermostatically controlled water bath shaker at 37 ± 0.5 °C for 2 h. After equilibration, samples were filtered through Whatman filter paper No. 1, and the dissolved drug concentration was determined spectrophotometrically [6].

Analytical Method Development

UV spectrophotometry was selected for preliminary drug analysis owing to the chromophores present in Nimesulide (aromatic rings and nitro groups). The drug exhibited a characteristic λmax within the range of 392–396 nm in 0.1 N HCl. A full scan (200–400 nm) was performed to confirm λmax.

Calibration Curve

A standard stock solution was prepared by dissolving 10 mg of Nimesulide in 100 mL of 0.1 N HCl. Aliquots equivalent to 3–28 µg/mL were prepared and their absorbances recorded at 266 nm. A calibration curve was plotted to establish linearity [7].

Micrometric Properties

Bulk and tapped density were determined using a 100 mL graduated cylinder. Carr's compressibility index and Hausner's ratio were calculated to assess flow properties. The angle of repose was determined using the fixed funnel method, with θ calculated as $\tan^{-1}(h/r)$ [8].

Formulation of Nimesulide 250 mg Immediate-Release Tablets

Composition per tablet:

- Nimesulide: 100 mg
- Lactose: 60 mg
- MCC: 30 mg
- Starch: 30 mg
- CMC: 10 mg
- Povidone K-30: 10 mg
- Magnesium stearate: 5 mg
- Talc: 3 mg

Procedure: Nimesulide tablets were prepared by confirming drug–excipient compatibility, followed by sieving (drug, lactose, MCC, starch through #40; lubricants through #60). The drug and diluents were dry mixed for 15 minutes, then granulated using a Povidone K-30 binder solution. The damp mass was dried, passed through a #20 mesh, blended with magnesium stearate and talc, and finally compressed into tablets using a rotary press with concave punches (8–10 mm).

Evaluation of Powder Blend (Pre-Compression Parameters)

The pre-compression parameters of the powder blend were evaluated to assess flowability and compressibility [9,10].

Angle of Repose

The angle of repose indicates the flowability of powder and is determined by the fixed funnel method. A funnel with a 10 mm stem was positioned 2 cm above a flat surface. Approximately 10 g of the blend was allowed to flow freely to form a conical pile. The radius (r) and height (h) of the heap were measured, and the angle (θ) was calculated using:

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Flow properties were interpreted as: excellent (<30°), good (30–34°), passable (35–40°), and poor (>40°).

Bulk Density and Tapped Density

Bulk density was determined by gently pouring 25 g of blend into a 100 mL graduated cylinder and recording the occupied volume. Tapped density was measured using a USP tap density tester after 500–1250 taps until constant volume was reached. These values provided information about the packing properties of the powder.

Carr's Compressibility Index

Carr's index evaluates compressibility and was calculated as:

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

Values below 15% indicate excellent flow, while >25% suggest poor flow.

Hausner's Ratio

Hausner's ratio is another flowability indicator and was calculated as:

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

Ratios ≤1.25 indicate good flow, while >1.5 indicates poor flow.

Evaluation of Tablets (Post-Compression Parameters)

The post-compression evaluation of Nimesulide tablets was carried out to determine uniformity, mechanical strength, disintegration behaviour, and drug release characteristics [11,12].

Hardness (Crushing Strength)

Five tablets from each batch were tested using an Electrolab digital hardness tester. Hardness was expressed in kg/cm². Adequate hardness ensures mechanical strength, while not being so high as to affect disintegration or dissolution.

Friability

Twenty pre-weighed tablets were rotated in a Roche friabilator at 25 rpm for 100 revolutions. After dedusting, tablets were reweighed, and friability (%F) was calculated:

$$\%F = \frac{W_1 - W_2}{W_1} \times 100$$

where W_1 = initial weight and W_2 = final weight. A friability <1% indicates acceptable resistance to abrasion.

Weight Variation

Twenty tablets were weighed individually using an analytical balance. Mean weight was calculated, and the percentage deviation of each tablet from the mean was determined. The results were compared with USP specifications (±7.5% for tablets 130–324 mg; ±5% for tablets >324 mg).

Thickness and Diameter

Tablet thickness and diameter were measured using Vernier callipers. Maintaining uniformity ensures batch-to-batch consistency and compatibility with packaging equipment.

Content Uniformity

Five tablets were powdered, and an amount equivalent to 10 mg of Nimesulide was dissolved in 0.1 N HCl, filtered, and diluted appropriately. Absorbance was recorded at 225 nm using a UV spectrophotometer. Drug content was calculated against a standard calibration curve. The acceptance criterion was 85–115% of the label claim.

In Vitro Dissolution Studies

Dissolution was performed using the USP Type II (paddle) apparatus in 900 mL of 0.1 N HCl maintained at 37 ± 0.5 °C with a 50 rpm paddle speed. Aliquots (10 mL) were withdrawn at predetermined intervals up to 24 h, filtered, and analysed at 266 nm. Withdrawn volume was replaced with fresh medium. The cumulative percentage drug release was calculated and plotted against time.

In-vivo Analgesic Studies

Animal Selection

Male Wistar rats (150–250 g) were selected for the study as they are widely used in pharmacological research due to their consistent physiology and ease of handling. Male rats were specifically chosen to avoid hormonal fluctuations that may affect pain perception. All experimental protocols were conducted in accordance with ethical guidelines and were approved by the Institutional Animal Ethics Committee (IAEC), ensuring compliance with CPCSEA norms [13,14].

Tail Flick Test

The tail flick test was employed to evaluate the analgesic activity of Nimesulide, a well-established model for determining central analgesic effects. In this method, the distal portion of the rat's tail was exposed to a radiant heat source, and the latency (reaction time in seconds) for the rat to flick its tail was recorded using a tail flick analgesia meter [1]. A cut-off time (30 sec) was set to prevent tissue injury.

The baseline reaction time was measured before drug administration and recorded as 2 seconds. Nimesulide was administered orally (p.o.) at a dose of 10 mg/kg, suspended in an appropriate vehicle. Control animals received vehicle (saline), and a positive control group was treated with diclofenac (10 mg/kg, i.p.). Reaction times were recorded at different time intervals post-administration (30 min, 35 min, and 1 h).

Results and Discussion

Organoleptic Properties

The organoleptic characteristics of Nimesulide, including colour, odour, and taste, were examined to ensure identity confirmation as per pharmacopeial standards. Results are presented in Table 1.

Table 1. Organoleptic properties of Nimesulide

Property	Observation
Colour	Yellow crystalline powder
Odour	Odourless
Taste	Slightly bitter

Solubility Studies

Solubility was assessed in different solvents at 37 ± 0.5 °C to determine suitability for formulation development. The solubility profile is shown in Table 2.

Table 2. Solubility of Nimesulide in Different Solvents

Solvent	Solubility (mg/mL)
Distilled Water	0.012 ± 0.001
0.1 N HCl	0.083 ± 0.003
Glacial Acetic Acid	1.24 ± 0.02
Anhydrous Ethanol	2.85 ± 0.04
Ethyl Acetate	1.63 ± 0.03

UV Spectrophotometric Analysis

UV scanning (200–400 nm) confirmed the presence of characteristic chromophores, with λmax identified at 294 nm in 0.1 N HCl. This complies with reported in Figure 1

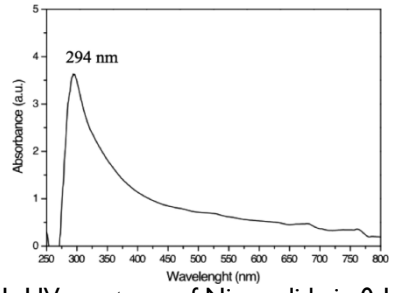

Figure 1. UV spectrum of Nimesulide in 0.1 N HCl showing λmax at 294 nm.

Calibration Curve

The calibration curve demonstrated linearity in the concentration range of 3–28 µg/mL with $R^2 = 0.999$, confirming suitability for quantitative analysis. The data are shown in Table 3 and the graph in Figure 2.

Table 3. Calibration curve data of Nimesulide

Concentration (µg/mL)	Absorbance (Mean ± SD)
3	0.094 ± 0.002
6	0.191 ± 0.003
9	0.282 ± 0.004
12	0.387 ± 0.005
15	0.478 ± 0.004
18	0.574 ± 0.006
21	0.669 ± 0.004
24	0.765 ± 0.005
28	0.893 ± 0.006

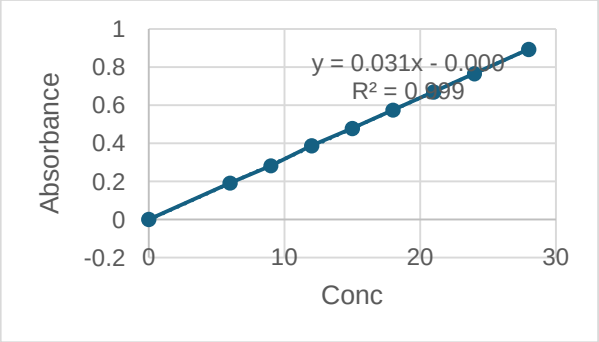

Figure 2. Calibration curve of Nimesulide in 0.1 N HCl ($R^2 = 0.999$).

Micrometric Properties

Micrometric analysis was carried out to evaluate the flowability and compressibility of the drug powder. Results are shown in Table 4.

Table 4. Micrometric properties of Nimesulide

Parameter	Mean ± SD)
Bulk Density (g/mL)	0.41 ± 0.02
Tapped Density (g/mL)	0.49 ± 0.01
Carr's Index (%)	16.3 ± 0.6
Hausner's Ratio	1.19 ± 0.02
Angle of Repose (°)	31.4 ± 0.8

Results and Discussion

The prepared Nimesulide tablets were subjected to a comprehensive evaluation covering both pre-compression and post-compression parameters to confirm the suitability of the formulation for large-scale production. Pre-compression studies revealed an angle of repose of 28.6° ± 0.8, which lies within the acceptable range (<30°), indicating good flowability of the granules and supporting their suitability for direct compression. Bulk density (0.45 ± 0.02 g/mL) and tapped density (0.52 ± 0.01 g/mL) were found to be consistent, yielding a Carr's index of 13.4 ± 1.2% and a Hausner ratio of 1.15 ± 0.01. These values confirm good flow and compressibility, ensuring uniform die filling and minimal weight variation during compression. Post-compression evaluation demonstrated that the tablets met pharmacopeial limits. The mean tablet weight was 198.6 ± 2.5 mg, with weight variation well below the ±7.5% limit as per USP standards, confirming dose uniformity [3]. The hardness value of 5.6 ± 0.4 kg/cm² ensured mechanical strength sufficient for handling and transport while maintaining patient acceptability. The thickness of 3.1 ± 0.1 mm was uniform, suggesting consistent die settings during compression. Friability was observed at 0.62 ± 0.05%, which is well below the acceptable limit of 1%, reflecting good mechanical resistance.

The disintegration time of 6.5 ± 0.4 min confirmed rapid breakdown of tablets in aqueous medium, meeting the pharmacopoeial requirement of disintegration within 15 minutes for immediate-release formulations. Drug content uniformity was 98.7 ± 1.3%, confirming homogeneous distribution of Nimesulide across tablets. Finally, the in-vitro drug release profile demonstrated 96.5 ± 2.1% release at 30 min, indicating rapid dissolution and potential for fast onset of action, making the formulation suitable for acute pain management. Collectively, these results establish that the optimised formulation met all quality standards and exhibited favourable characteristics for clinical use.

Table 4: Pre-compression and Post-compression Evaluation of Nimesulide Tablets

Parameter	Result (Mean ± SD)
Pre-compression Parameters	
Angle of Repose (°)	28.6 ± 0.8
Bulk Density (g/mL)	0.45 ± 0.02
Tapped Density (g/mL)	0.52 ± 0.01
Carr's Index (%)	13.4 ± 1.2
Hausner Ratio	1.15 ± 0.01
Post-compression Parameters	
Weight Variation (mg)	198.6 ± 2.5
Hardness (kg/cm²)	5.6 ± 0.4
Thickness (mm)	3.1 ± 0.1
Friability (%)	0.62 ± 0.05
Disintegration Time (min)	6.5 ± 0.4
Drug Content Uniformity (%)	98.7 ± 1.3
In-vitro Drug Release (%) at 30 min	96.5 ± 2.1

In-vivo Analgesic Studies

The results demonstrated a significant, time-dependent increase in tail flick latency following Nimesulide administration. At 30 min, the latency increased to 8

sec, which further increased to 17 sec at 35 min and reached 27 sec at 1 h, indicating enhanced analgesic activity. This increase in reaction time reflects a central analgesic effect, likely mediated via inhibition of prostaglandin synthesis and modulation of inflammatory mediators (Table 5).

Table 5: The effect of Nimesulide on pain threshold in rats

Time Interval	Response Time (sec)
Baseline (before dose)	2
30 minutes	8
35 minutes	17
1 hour	27

Conclusion

The study successfully developed and evaluated Nimesulide tablets with favorable physicochemical and pharmacological properties. Pre- and post-compression analyses confirmed formulation stability and uniformity, while in vitro release demonstrated rapid drug availability, essential for acute pain therapy. In vivo studies further substantiated the analgesic potential of Nimesulide, significantly enhancing pain threshold in animal models. These findings reaffirm its efficacy, tolerability, and therapeutic relevance, establishing Nimesulide as a dependable option in acute pain management.

Author Contributions

Vemula Prasanth: Conceptualisation, Methodology, Data curation, Writing – original draft.Vadlamudi Rangarao: Formal analysis, Investigation, Validation.Vasana Naga Durga Deekshitha: Software, Data interpretation, Visualisation.Gayathri Veerla: Method development, Literature review, Writing – review & editing.Patibandla Jahnavi: Supervision, Project administration, Final manuscript approval.

Conflict of Interest

The authors declare that there is no conflict of interest

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