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A COMPREHSENSIVE REVIEW ON ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR NAPROXEN AND PARACETAMOL IN BULK AND PHARMACEUTICAL DOSAGE FORMS

Shanmugapriya C.*, Dr. P. Aravanan, Vaishali Padmasri T., Sudharsan R., Dr. D. Dachinamoorthy

Department of Pharmaceutical Analysis, Sree Abirami College of Pharmacy, Coimbatore-21, (Affiliated to The Dr. M.G.R Medical University, Chennai.)

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***Corresponding Author: Shanmugapriya C.**
Department of Pharmaceutical Analysis, Sree Abirami College of Pharmacy, Coimbatore-21, (Affiliated to The Dr. M.G.R Medical University, Chennai.) **DOI:** https://doi.org/10.5281/zenodo.23798667

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ABSTRACT

The treatment of pain, inflammation, and fever, naproxen and paracetamol are commonly used analgesic and antipyretic medications that can be taken alone or in combination. For quality assurance, regulatory compliance, and therapeutic efficacy, these medications must be accurately quantified in bulk and pharmaceutical dosage forms. With a particular focus on reversed-phase high-performance liquid chromatography (RP-HPLC) and ultraviolet (UV) spectrophotometric techniques for the quantification of naproxen and paracetamol, this study critically reviews current advancements in analytical procedures. Key chromatographic parameters (stationary phase, mobile phase composition, flow rate, detection wavelength, and retention times), ICH-recommended validation parameters (linearity, accuracy, precision, specificity, robustness, LOD, and LOQ), and applications to commercial formulations are compiled from published research. Additionally covered are simultaneous estimating techniques for combinations such paracetamol–ibuprofen, sumatriptan–naproxen, and paracetamol–naproxen. The methods under consideration exhibit simplicity, sensitivity, accuracy (recoveries usually 97–102%), and precision (RSD ≤ 2%), which qualify them for regular quality monitoring. Future directions toward greener, faster, and stability-indicating methodologies are discussed, along with the shortcomings of current systems.

KEYWORDS: Naproxen, Paracetamol, RP-HPLC, UV Spectrophotometry, Method Validation, ICH Guidelines, Pharmaceutical Analysis.

INTRODUCTION

Naproxen is a non-steroidal anti-inflammatory medicine (NSAID) that is a member of the 2-arylpropionic acid class. Its chemical formula is (+) - (S)-2-(6-methoxynaphthalen-2-yl) propanoic acid. It mainly reduces prostaglandin synthesis by inhibiting cyclooxygenase enzymes, which results in analgesic, anti-inflammatory, and antipyretic effects. It is recommended for gout, ankylosing spondylitis, rheumatoid arthritis, osteoarthritis, and related disorders. Chemically known as N-(4-hydroxyphenyl) acetamide, paracetamol (acetaminophen) is a common over-the-counter antipyretic and analgesic with minimal anti-inflammatory properties. It is frequently co-formulated with various medicines and is favoured in individuals who are prone to gastrointestinal discomfort.

In order to guaranty the identification, stability, potency, and purity of these medications, pharmaceutical analysis is essential. A variety of methods, such as UV spectrophotometry, HPLC, HPTLC, and LC-MS, are revealed in the literature. Nevertheless, a lot of documented techniques are costly, time-consuming, or complicated. For routine quality control of bulk drugs and completed dosage forms, straightforward, quick, accurate, and economical approaches verified in accordance with ICH, USP, and FDA requirements are still greatly desired. This review summarizes recent research on the development and validation of analytical methods for naproxen and paracetamol using RP-HPLC and UV spectrophotometric techniques, including simultaneous estimation in multi-component formulations. Chromatographic/spectroscopic conditions, validation results, and practical applicability are highlighted.

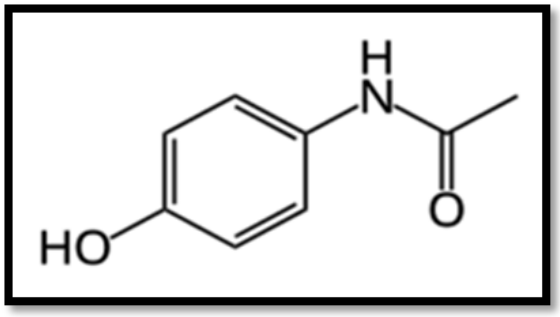

Figure 1: Structure of Paracetamol.

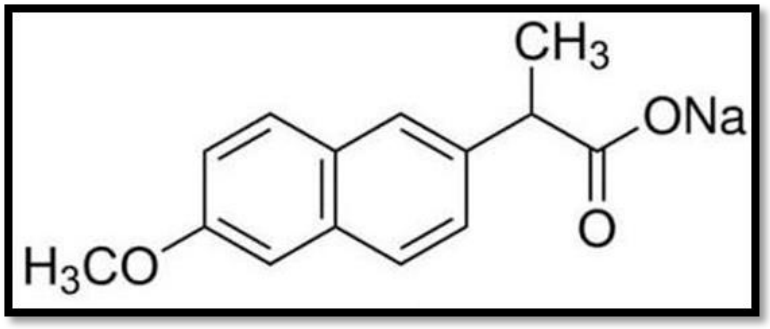

Figure 2: Structure of Naproxen Sodium.

ANALYTICAL METHODS FOR NAPROXEN

RP-HPLC METHODS

A C18 column (250 × 4.6 mm, 5 µm) with a mobile phase of dibasic sodium phosphate buffer (pH 7.80, adjusted with sodium hydroxide) and acetonitrile (70:30, v/v) at a flow rate of 0.7 mL/min and UV detection at 225 nm was used in a straightforward RP-HPLC technique for naproxen in pharmaceutical dosage forms. The duration of retention was 4.8 ±

0.1 minutes. Over the examined range, the technique was linear (r^2 = 0.9991), with recovery >97% and intra- and inter-day precision within acceptable bounds (RSD% ≤ 2.0). Studies on specificity verified that there was no excipient interference. The technique was successfully used on tablets that were sold.

Using a C8 column (4.6 × 150 mm, 3.5 µm) with buffer: acetonitrile (50:50) at 0.7 mL/min and detection at 285 nm, another RP-HPLC technique allowed for the simultaneous measurement of sumatriptan and naproxen. Sumatriptan and naproxen had retention durations of roughly 5.87 and 2.24 minutes, respectively. The range of 60–100 µg/mL showed linearity (r = 0.999). Recoveries of 99.0–101.0% were obtained from accuracy studies at 50%, 100%, and 150% levels. Both analytes had stated LOD and LOQ values, and the percentage RSD was less than 2%. ICH standards were satisfied in terms of system appropriateness, robustness, and ruggedness.

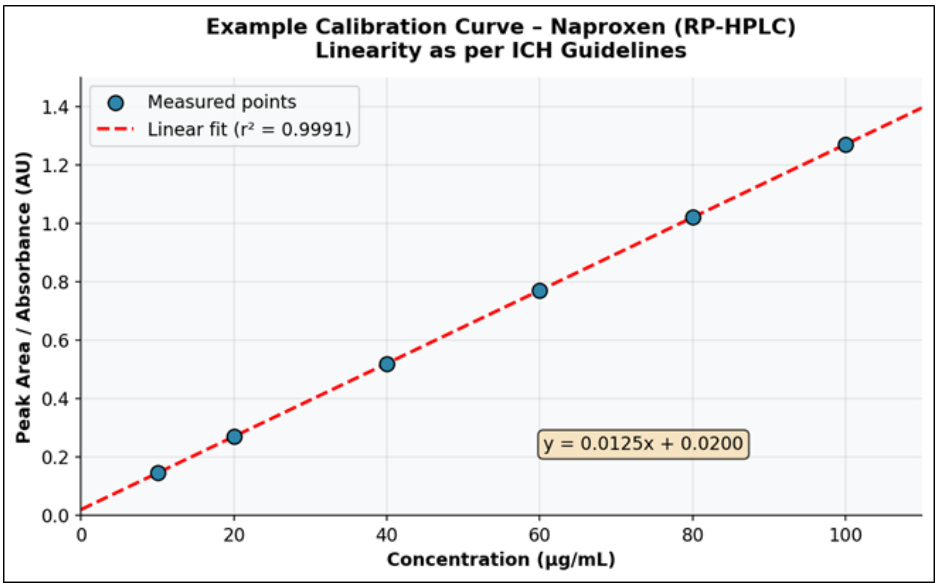

Figure 1: Example Calibration Curve – Naproxen (RP-HPLC) showing excellent linearity (r^2 = 0.9991)

UV SPECTROPHOTOMETRIC METHODS

A UV spectrophotometric technique for naproxen in bulk and tablet forms was established and validated following ICH standards. Methanol, ethanol, DMF, or acetone-based solvent systems were enhanced. The approach assessed specificity, linearity, precision, accuracy, and robustness. Analysis of commercial tablets (Naproxen IP 750 mg and Naproxen Sodium USP 550 mg) showed uniform and accurate outcomes, validating their appropriateness for standard quality assessment. The method is straightforward, economical, and lacks major disruption.

ANALYTICAL METHODS FOR PARACETAMOL

RP-HPLC METHODS

A validated RP-HPLC method for the simultaneous determination of paracetamol and naproxen employed an Eclipse XDB C18 column (150 × 4.6 mm, 5 µm) with a gradient mobile phase of water (pH 2.5 adjusted using orthophosphoric acid): acetonitrile, beginning at 87:13 and programmed accordingly, at a flow rate of 1.0 mL/min and detection at 263 nm. Retention times were around 3.0 minutes for paracetamol and 7.4 minutes for naproxen. The linearity ranges were 5 - 80 µg/mL for paracetamol and 3 - 48 µg/mL for naproxen. Average recoveries were 99.72% and 100.88%, correspondingly. Intermediate precision demonstrated an acceptable %RSD. The approach is appropriate for quality assurance of fixed-dose combination tablets.

A simple RP-HPLC method for paracetamol employed a C18 column (4.6 × 250 mm, 5 µm) with a mobile phase of acetonitrile: water (25:75, v/v; adjusted to pH 3.5 using orthophosphoric acid) at a flow rate of 1 mL/min and detection at 207 nm. Modifying solvent ratios and flow rates resulted in a retention time of about 3.6 min under the selected conditions. Linearity, accuracy, precision (repeatability, intra-day, inter-day), LOD (120 ng/mL), and LOQ (360 ng/mL) were assessed. Recoveries and assay results were between 99–102%. An isocratic RP-HPLC method for simultaneous quantification of paracetamol and ibuprofen employed acetonitrile: phosphate buffer (pH 3.0) (60:40, v/v) with PDA detection in the 220–230 nm spectrum. Retention times were approximately 2.5 minutes (paracetamol) and 5.2 minutes (ibuprofen). Linearity varied from 10 to 100 µg/mL for the two drugs (r > 0.999). Compulsory degradation tests confirmed the method's capacity to reflect stability. Metrics for accuracy, precision, robustness, and sensitivity complied with ICH Q2(R1) guidelines.

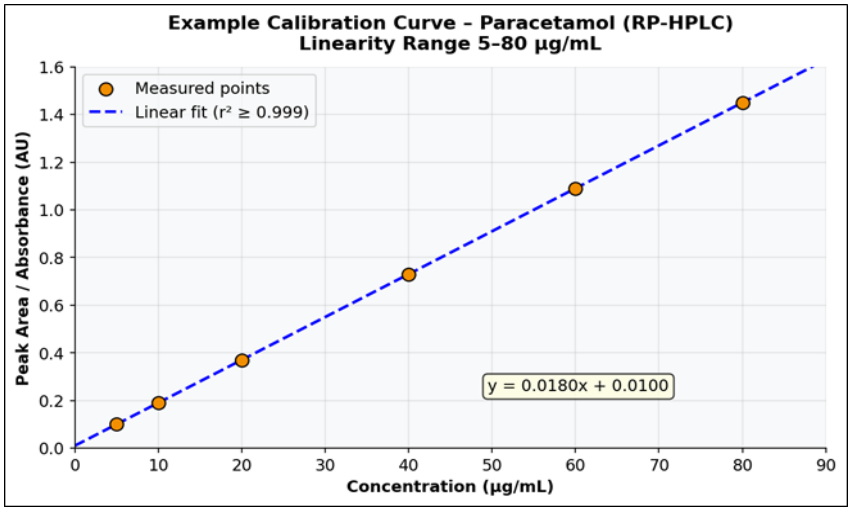

Figure 2: Example Calibration Curve – Paracetamol (RP-HPLC) Linearity Range 5–80 µg/mL

UV-VISIBLE SPECTROPHOTOMETRIC METHODS

A UV-visible spectrophotometric technique for assessing paracetamol tablets utilized methanol and water as solvents. Parameters were chosen and confirmed in line with ICH Q2(R1) guidelines, incorporating statistical assessment of RSD and %RSD. The approach is innovative, secure, precise, and unaffected by interference, endorsing its application for regular testing of tablet formulations.

Drug / Combination	Method	Column / Conditions	Detection	Retention Time	Key Validation
Naproxen	RP-HPLC	C18; Buffer (pH 7.8): ACN (70:30)	225 nm	4.8 min	r^2=0.9991; Recovery >97%; RSD ≤2%
Sumatriptan + Naproxen	RP-HPLC	C8; Buffer: ACN (50:50)	285 nm	Nap 2.24 / Sum 5.87 min	r=0.999; Recovery 99–101%
Naproxen	UV Spectrophotometry	Methanol/Ethanol/DMF/Acetone	UV range	—	ICH validated
Paracetamol + Naproxen	RP-HPLC (Gradient)	Eclipse XDB C18; Water (pH 2.5): ACN	263 nm	PCM ~3.0 / Nap ~7.4 min	Linearity & Recovery ~100%
Paracetamol	RP-HPLC	C18; ACN: Water (25:75, pH 3.5)	207 nm	~3.6 min	LOD 120 ng/mL; LOQ 360 ng/mL

Paracetamol + Ibuprofen	RP-HPLC (Isocratic)	ACN: Phosphate buffer (60:40)	220–230 nm	PCM ~2.5 / Ibu ~5.2 min	Stability-indicating; ICH compliant
Paracetamol	UV-Visible	Methanol & Water	UV-Vis	—	ICH Q2(R1) validated

DISCUSSION

In the studies analysed, RP-HPLC is recognized as the favoured method for analysing both single and multiple components due to its enhanced resolution, sensitivity, and capability to distinguish analytes from excipients and possible degradation products. Common stationary phases include C18 or C8 columns; mobile phases usually mix aqueous buffers (phosphate or modified with orthophosphoric acid) with acetonitrile in ratios tailored for retention and peak shape. Detection wavelengths vary from 207 to 285 nm based on the chromophore and matrix. Flow rates ranging from 0.7 to 1.0 mL/min and either ambient or regulated column temperatures are commonly used. UV spectrophotometric techniques provide ease of use, reduced expenses, and quick analysis for single-drug tests or when chromatographic instruments are not accessible. Nevertheless, their effectiveness is constrained in multi-component formulations with overlapping spectra unless derivative or simultaneous-equation methods are utilized. Validation results consistently satisfy ICH standards: linearity with strong correlation coefficients ($r^2 \geq 0.999$), accuracy with recoveries close to 100%, precision with RSD ≤ 2%, and sufficient sensitivity (low LOD/LOQ). Studies on specificity verify that there is no interference from typical tablet excipients. Studies on forced degradation in certain reports demonstrate stability-indicating capability, which is becoming increasingly necessary for regulatory submissions. Ongoing challenges involve the necessity for more eco-friendly mobile phases (lower organic solvent use), quicker run times, and techniques that can accurately quantify degradation products at minimal concentrations. Expanding validated techniques to biological matrices or more intricate fixed-dose combinations would increase their usefulness.

CONCLUSION

The evaluated RP-HPLC and UV spectrophotometric techniques offer dependable, validated methods for the quantitative analysis of naproxen and paracetamol in bulk and pharmaceutical formulations. RP-HPLC techniques, especially those allowing concurrent analysis, provide excellent precision, accuracy, and specificity ideal for regular quality control and stability assessments. UV techniques continue to be appealing due to their straightforwardness and cost-effectiveness in analysing single drugs. Ongoing advancement of fast, environmentally friendly, and completely stability-indicating methods will reinforce continuous pharmaceutical quality assurance and regulatory adherence.

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