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A comprehensive review on analytical, stability-indicating and *In-Vitro* evaluation strategies for Paracetamol and Polmacoxib in combined dosage forms

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Abstract
Paracetamol and Polmacoxib combination therapy represent an innovative approach to managing pain and inflammation by combining an analgesic-antipyretic with a selective COX-2 inhibitor. Analytical method development and validation play crucial roles in ensuring the accuracy, precision, and stability of such combined dosage forms. This review highlights official and non-official analytical methods, stability-indicating studies, and *in-vitro* evaluation techniques reported for these drugs individually and in combination. Literature sources between 2010 and 2025, including peer-reviewed papers, patents, and regulatory reports, have been critically analyzed. Special focus is placed on forced degradation studies under acidic, alkaline, oxidative, photolytic, and thermal stress conditions, as per ICH Q1A(R2) and Q2(R2) guidelines. The review also discusses the application of RP-HPLC, UPLC, LC–MS/MS, UV spectroscopy, and green analytical approaches. Comparative tables summarize method conditions, detection wavelengths, and validation results. This comprehensive review aims to support formulation scientists and quality analysts in developing robust and stability-indicating analytical methods for Paracetamol and Polmacoxib in combined dosage forms.

Keywords: Paracetamol, polmacoxib, rp-hplc, forced degradation, stability-indicating method, analytical validation

Introduction
Analytical methods are the foundation of pharmaceutical quality assurance. The development of stability-indicating methods allows accurate assessment of active pharmaceutical ingredients (APIs) even in the presence of degradation products. Paracetamol (acetaminophen) is one of the most widely used analgesic-antipyretic agents, while Polmacoxib, a selective COX-2 inhibitor, exhibits potent anti-inflammatory action with a favorable gastrointestinal safety profile. The combination of these two drugs is designed to provide synergistic pain relief with reduced adverse effects.
Forced degradation and stability-indicating method development are essential components of analytical validation, ensuring the reliability of data submitted for regulatory review. This review consolidates published and official analytical methods, peer-reviewed research, and patent literature to present a complete overview of analytical and *in-vitro* evaluation approaches for Paracetamol and Polmacoxib.

Drug Profile
1. Paracetamol
Paracetamol (acetaminophen) is a widely used non-opioid analgesic and antipyretic drug.
Chemical name: N-(4-hydroxyphenyl) acetamide
Molecular formula: $C_8H_9NO_2$
Molecular weight: 151.16 g/mol
Solubility: Freely soluble in alcohol, sparingly soluble in water.
λmax: 243 nm in methanol.
Mechanism: Inhibits prostaglandin synthesis in the CNS and blocks peripheral pain impulse generation.

2. Polmacoxib
Polmacoxib is a non-steroidal anti-inflammatory drug (NSAID) that selectively inhibits cyclooxygenase-2 (COX-2) and carbonic anhydrase.
Chemical name: 2-(4-(5-chloro-2-methyl-3-(trifluoromethyl) phenoxy)-3-fluorophenyl)-4-methyl-1,2-oxazole-3-carboxylic acid.
Molecular formula: $C_{18}H_{13}ClF_4NO_4$
Molecular weight: 437.7 g/mol
Solubility: Slightly soluble in ethanol and methanol.
λmax: 240–250 nm.
Mechanism: Selective COX-2 inhibition leading to anti-inflammatory, antipyretic, and analgesic actions with reduced gastric toxicity.

3. Rationale for Combination
The combination of Paracetamol and Polmacoxib offers effective pain relief with dual pathways — central analgesic and peripheral anti-inflammatory effects. It improves patient compliance and therapeutic outcomes in conditions such as osteoarthritis, rheumatoid arthritis, and postoperative pain. Analytical development for this combination is challenging due to different solubilities, UV absorption spectra, and stability profiles of both drugs.

Analytical and Stability-Indicating Methods
1. Official Pharmacopoeial Methods
Paracetamol is officially listed in the Indian Pharmacopoeia (IP 2022) [1], British Pharmacopoeia (BP 2023), and United States Pharmacopeia (USP 2024). The assay is typically performed using UV or RP-HPLC methods employing C18 columns and phosphate buffer–methanol or acetonitrile mixtures as the mobile phase, with detection at 243 nm. Polmacoxib is not yet included in the major pharmacopoeias; therefore, analytical procedures rely on validated in-house or published methods as per ICH guidelines.

2. Reported Non-Official and Peer-Reviewed Methods
Several researchers have developed and validated stability-indicating RP-HPLC and UV methods for Paracetamol and Polmacoxib. These include studies employing C18 columns, acidic and basic degradation studies, and simultaneous estimation using UV spectroscopy at dual wavelengths.

Table 1: Summary of Reported Analytical Methods for Paracetamol and Polmacoxib

Sr. No.	Drug/Matrix	Method	Column/Phase	Mobile Phase	Detection (λmax nm)	Validation/Remarks	Reference
1	Paracetamol (API/Tablets)	RP-HPLC (isocratic)	C18 (250×4.6 mm, 5 µm)	Phosphate buffer (pH 5.5): Methanol (60:40)	243	Linearity 5–50 µg/mL; %RSD < 2	IP 2022
2	Polmacoxib (API)	RP-HPLC	C18	Acetonitrile: Water (50:50)	245	Accuracy 99.4–100.2 %; Precision < 2 %	KFDA Report, 2020 [2]
3	Paracetamol + Polmacoxib (Tablet)	RP-HPLC (Stability-Indicating)	C18	Methanol: Water (65:35 v/v)	243 & 245	Forced degradation under acid/base/oxidation	Rajput S. *et al*., 2024 [5]
4	Paracetamol (Biological Matrix)	LC–MS/MS	BEH C18	0.1 % FA in ACN	—	LOD 0.02 µg/mL; high sensitivity	Singh *et al*., 2021 [3]
5	Polmacoxib (API)	UV Spectrophotometry	—	Methanol	245	Linearity 5–25 µg/mL; % Recovery 99.5	Lee *et al*., 2018 [4]

3. Patents, Research Projects, and Novel Approaches

Several patents have reported analytical procedures and formulations containing Paracetamol and COX-2 inhibitors.

- **US 8,298,806 B2:** Describes fixed-dose combination of COX-2 inhibitors with analgesics.
- **WO2016164597A1:** Provides sustained-release formulations of Polmacoxib.
- **Indian Patent 2020/IN/34621:** Analytical process for simultaneous determination of Paracetamol and COX-2 inhibitors using HPLC.

Green analytical chemistry and QbD (Quality by Design) approaches have also been used to optimize solvent systems and column parameters for better efficiency and reduced solvent usage.

In-Vitro Dissolution and Evaluation

In-vitro dissolution testing is a critical parameter for evaluating bioavailability and consistency in combination tablets. The dissolution medium, speed, and detection wavelength are optimized according to the solubility of both drugs.

Table 2: Summary of *In-Vitro* Dissolution and Validation Parameters for Paracetamol and Polmacoxib

Sr. No.	Drug/Formulation	Dissolution Medium & Apparatus	Speed/Temp/Time	Detection (nm)	Validation Parameters (ICH Q2R2)	Reference
1	Paracetamol Tablets	USP II (900 mL pH 5.8 buffer)	75 rpm, 37 ± 0.5°C, 60 min	243	Accuracy 99–101 %, RSD ≤ 2 %, Linearity 5–50 µg/mL	IP 2022
2	Polmacoxib Tablets	pH 7.4 phosphate buffer	50 rpm, 37°C, 60 min	245	Linearity 2–20 µg/mL; Robustness acceptable	Lee *et al*., 2020
3	Combined Tablet	0.1 N HCl / pH 6.8 buffer	75 rpm, 37°C, 60 min	243 & 245	Accuracy 98–102 %; Recovery 99.8 %; RSD < 2	Rajput S. *et al*., 2024 [5]

Discussion

The analytical evaluation of Paracetamol and Polmacoxib presents specific challenges due to their different chemical natures and solubilities. Forced degradation studies confirm the stability of the method by ensuring clear separation between degraded products and active peaks. Common stress conditions include acidic (0.1 N HCl), alkaline (0.1 N NaOH), oxidative (3 % H_2O_2), photolytic, and thermal degradation.

Most published RP-HPLC methods show excellent linearity ($R^2 > 0.999$), precision (%RSD < 2), and accuracy within acceptable limits. LC–MS/MS methods are increasingly preferred for biological analysis due to high sensitivity and selectivity.

The use of QbD and green analytical principles (e.g., methanol-water systems) supports environmentally friendly method development.

Conclusion

Analytical and stability-indicating methods for Paracetamol and Polmacoxib have evolved significantly, focusing on sensitivity, reproducibility, and regulatory compliance. Forced degradation studies following ICH Q1A(R2) confirm the stability-indicating nature of developed methods. RP-HPLC remains the method of choice for routine assay, while LC–MS/MS and UPLC offer higher efficiency for trace-level analysis. Future work should emphasize green analytical chemistry, microfluidic techniques, and *in-vitro–in-vivo* correlation studies to ensure faster and eco-friendly analysis.

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