

Development and Validation of a Simultaneous RP-HPLC Method for the Estimation of Polmacoxib and Paracetamol in Combined Tablet Dosage Form

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Abstract

Background: Paracetamol and Polmacoxib are used in combination for the management of pain and inflammation associated with osteoarthritis. A simple and reliable analytical method is required for their simultaneous estimation in combined tablet dosage form.

Objective: To develop and validate a simple, accurate, precise, and economical RP-HPLC method for the simultaneous estimation of Polmacoxib and Paracetamol in combined tablet dosage form.

Methods: Chromatographic separation was carried out on a Hibar ODS C18 column. The mobile phase consisted of acetonitrile and 0.1% orthophosphoric acid in water (80:20 v/v), pH 4.5. The analysis was performed at a flow rate of 1.0 mL/min, with detection at 225 nm using a UV detector. The developed RP-HPLC method was validated according to ICH guidelines by evaluating specificity, linearity, precision, accuracy, limit of detection (LOD), and limit of quantification (LOQ).

Results: The developed RP-HPLC method showed good chromatographic separation of Paracetamol and Polmacoxib, with retention times of 3.39 min and 5.92 min, respectively. The method exhibited excellent linearity over the concentration range of 325-975 µg/mL for Paracetamol and 2-6 µg/mL for Polmacoxib, with correlation coefficients of approximately 0.999. Accuracy studies demonstrated recovery values within the acceptable range of 98-102%, while precision studies showed %RSD values below 2%, indicating good reproducibility. The method was found to be robust and sensitive, with satisfactory LOD and LOQ values, and was successfully applied to the assay of marketed formulations, producing results within acceptable limits.

Conclusion: A simple, rapid, accurate, and precise RP-HPLC method was successfully developed and validated for the simultaneous estimation of Paracetamol and Polmacoxib in combined tablet dosage form. The proposed method is suitable for routine quality control analysis.

Keywords: Paracetamol; Polmacoxib; Method validation; RP-HPLC; ICH guidelines; Quantitative analysis

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Introduction

Paracetamol is chemically known as N-(4-hydroxyphenyl) acetamide. It is a widely used over-the-counter analgesic (pain reliever) and antipyretic (fever-reducing) drug. It is commonly used for the treatment of headache, fever, and other minor aches and pains, and is also an important ingredient in many cold and flu formulations¹. The onset of analgesic action occurs approximately 11 minutes after oral administration. Paracetamol is the active metabolite of phenacetin, which was previously used as an analgesic and antipyretic agent. Unlike phenacetin, paracetamol is not considered carcinogenic at therapeutic doses. It is believed to inhibit the activity of cyclooxygenase (COX) enzymes, and recent studies suggest that it shows a relatively high selectivity toward COX-2. Although paracetamol possesses analgesic and antipyretic effects comparable to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), its peripheral anti-inflammatory activity is limited, partly due to the high levels of peroxides present at sites of inflammation^{2,3}.

Polmacoxib (Fig. 2) is chemically known as 4-[3-(3-fluorophenyl)-4,5-dihydro-5,5-dimethyl-4-oxo-2-furanyl] benzene sulfonamide. It is a novel nonsteroidal anti-inflammatory drug (NSAID) used mainly for the management of pain and inflammation associated with osteoarthritis and other musculoskeletal disorders^{3,4}. Polmacoxib exhibits anti-inflammatory, analgesic, and antipyretic activities, and acts by selectively inhibiting the cyclooxygenase-2 (COX-2) enzyme, thereby reducing the synthesis of prostaglandins responsible for

pain and inflammation. Compared with conventional NSAIDs, selective COX-2 inhibitors may produce less gastrointestinal irritation and ulceration. In addition to COX-2 inhibition, polmacoxib has been reported to possess carbonic anhydrase binding properties, which may contribute to its pharmacological profile. Because of its potent anti-inflammatory activity and improved gastrointestinal safety profile, polmacoxib has gained attention as a useful therapeutic option in inflammatory and painful conditions^{5,6}.

Polmacoxib is a selective cyclooxygenase-2 (COX-2) inhibitor used for the management of pain and inflammation associated with osteoarthritis and other musculoskeletal disorders. Paracetamol is a widely used analgesic and antipyretic agent with a favorable safety profile. The combination of Polmacoxib and Paracetamol is used to provide enhanced analgesic and anti-inflammatory effects in the treatment of painful conditions. For the quality control of pharmaceutical dosage forms, accurate and reliable analytical methods are required for the simultaneous estimation of both drugs. RP-HPLC is one of the most commonly used analytical techniques due to its high sensitivity, specificity, precision, and reproducibility. A review of the literature revealed that only limited analytical methods have been reported for the simultaneous estimation of Polmacoxib and Paracetamol in combined dosage forms. Therefore, the present study was undertaken to develop a simple, accurate, precise, and economical RP-HPLC method for the simultaneous estimation of Polmacoxib and

Paracetamol in tablet dosage form and to validate the developed method according to ICH guidelines ^{7,8}.

1. Materials and Methods

1.1 Chemicals and Reagents

Paracetamol and Polmacoxib working standards with high purity were obtained from a certified pharmaceutical source. Methanol (HPLC grade), acetonitrile (HPLC grade), potassium dihydrogen phosphate, and orthophosphoric acid were procured from Merck (India). Deionized ultrapure water was supplied through a Milli-Q purification system. The phosphate buffer used in the mobile phase was prepared using potassium dihydrogen phosphate, and the pH was adjusted to 5.5 with orthophosphoric acid. Methanol was used as the diluent for the preparation of standard and sample solutions.

1.2 Instrumentation

The HPLC system consisted of a binary HPLC pump equipped with a manual/auto sampler programmed for a 20 μ L injection volume. Detection was carried out using a PDA/UV detector, and the chromatographic data were processed using the associated chromatography software. Separation was achieved on a Hibar ODS C18 column (250 mm $\times$ 4.6 mm, 5 μ m) under isocratic conditions. The mobile phase consisted of acetonitrile and 0.1% orthophosphoric acid in water in the ratio of 80:20 (v/v), with the pH adjusted to 4.5. The flow rate was maintained at 1.0 mL/min, and detection was performed at 225 nm. The mobile phase was filtered through a 0.45 μ m membrane filter and degassed before use. The injection volume was 20 μ L, and the analysis was carried out at ambient temperature.

1.3 Standard Solutions Preparation

A master stock solution of Paracetamol (PCM) was prepared by accurately weighing 100 mg of PCM and dissolving it in methanol in a 100 mL volumetric flask to obtain a concentration of 1000 μ g/mL. From this stock solution, 32.5 mL was transferred into a 100 mL volumetric flask and the volume was made up to the mark with methanol to obtain a working standard solution of 325 μ g/mL. Similarly, a master stock solution of Polmacoxib (POL) was prepared by accurately weighing 20 mg of POL and dissolving it in methanol in a 100 mL volumetric flask to obtain a concentration of 200 μ g/mL. From this stock solution, 1 mL was transferred into a 100 mL volumetric flask and the volume was made up to the mark with methanol to obtain a working standard solution of 2 μ g/mL ^{9,10}.

1.4 Optimization of HPLC Method

Both drugs were subjected to chromatographic analysis using different mobile phase compositions, pH values, and flow rates under various chromatographic conditions. The changes in retention time, peak shape, resolution, and theoretical plates were carefully observed. Initially, methanol and water in different ratios were tried, but satisfactory chromatographic separation was not obtained. Subsequently, acetonitrile and water in various ratios were evaluated, and satisfactory peak shape and separation of Paracetamol and Polmacoxib were observed. Further optimization was carried out using 0.1% orthophosphoric acid in water and acetonitrile. It was found that the mobile phase consisting of acetonitrile and 0.1% orthophosphoric acid in water (80:20, v/v), adjusted to pH 4.5, at a flow rate of 1.0 mL/min, provided good peak shape,

adequate theoretical plates, satisfactory resolution, and acceptable retention of 3.39 min for Paracetamol and 5.95 min for Polmacoxib. Therefore, these chromatographic conditions were selected as the optimized conditions for further validation studies ^{11,12}.

1.5 Method Validation

1.5.1 Specificity

The specificity of the method was assessed from the chromatograms, where complete separation of Paracetamol and Polmacoxib was achieved. The peaks obtained were sharp, symmetrical, and well resolved at the baseline. No interference from tablet excipients, impurities, or other formulation components was observed at the retention times of Paracetamol and Polmacoxib, indicating that the method is specific for the simultaneous estimation of both drugs ^{13,14}.

1.5.2 Linearity

The linearity of the method was evaluated by injecting six different concentrations of Paracetamol and Polmacoxib prepared in the mobile phase. The concentration range for Paracetamol was 325–975 μ g/mL, while for Polmacoxib it was 2–6 μ g/mL. Each concentration was injected in triplicate into the HPLC system while keeping the injection volume constant. The corresponding peak areas were recorded and plotted against their respective concentrations to construct the calibration curves ^{14,15}.

1.5.3 Precision

The precision of the method was evaluated in terms of repeatability and intermediate precision. Repeatability was assessed by analyzing three different concentrations of Paracetamol (325, 650, and 975 μ g/mL) and Polmacoxib (2, 4, and 6 μ g/mL) six times on the same day under the optimized chromatographic conditions. The peak areas were recorded and the percentage relative standard deviation (%RSD) was calculated. Intermediate precision was determined by repeating the analysis of the same concentrations on three different days ^{16,17}.

1.5.4 Accuracy

Accuracy of the HPLC method was evaluated by recovery studies using the standard addition technique, spiking pre-analyzed tablet formulation with PCM and POL standards at 80%, 100%, and 120% levels. Samples were prepared and analyzed in triplicate under optimized conditions, and peak areas were recorded to calculate percentage recovery. Tablet and standard stock solutions were prepared in methanol, filtered, and diluted to obtain working solutions. Different volumes of standard solution were added to the tablet solution to achieve the required concentration levels, and total concentrations corresponding to unspiked, 80%, 100%, and 120% levels were analyzed ¹⁸.

1.5.5 Limit of Detection (LOD) and Limit of Quantification

LOQ

The LOD and LOQ were determined based on signal-to-noise ratios of 3:1 for LOD and 10:1 for LOQ. Serial dilutions of mixed standard solutions of Paracetamol and Polmacoxib were prepared from the respective stock solutions using the mobile phase. The diluted solutions were injected into the HPLC system, and the concentrations corresponding to the required signal-to-noise ratios were considered as the LOD and LOQ for each drug. LOD and LOQ were also calculated statistically using the formulae $LOD = 3.3 \times \sigma/S$ and $LOQ = 10 \times \sigma/S$ ¹⁸.

1.5.6 Assay

A standard solution was prepared by dissolving PCM and POL in methanol, followed by dilution to obtain working concentrations. A sample solution was prepared from tablet powder, sonicated, diluted, and filtered to remove excipients. Both standard and sample solutions were injected into the HPLC system, and peak areas were recorded. The assay was calculated by comparing the peak areas of the sample and standard using the formula: $\% \text{ Assay} = (AT / AS) \times (CS / CT) \times 100$ ¹⁸.

2. Results

2.1 Specificity

The specificity of the developed HPLC method was confirmed by analyzing individual standard solutions of Paracetamol (PCM) and Polmacoxib (POL). Each drug exhibited distinct and well-defined peaks at their respective retention times. Peak identification was performed by comparing these retention times, and no interfering peaks were observed. The chromatograms showed well-resolved peaks, demonstrating that the method is specific and suitable for accurate identification of both analytes.

2.2 Linearity

The developed HPLC method showed good linearity over the concentration range of 325–975 µg/mL for Paracetamol (PCM) and 2–6 µg/mL for Polmacoxib (POL). Calibration curves were constructed by plotting peak area versus concentration, with correlation coefficients (R^2) close to 1 for both analytes, indicating excellent linear relationships. The chromatograms at different levels showed consistent and proportional responses, and the linearity range encompasses the accuracy study levels, confirming the method range.

Table 1: Linearity Data of PCM

S. No.	Concentration (µg/mL)	Mean Area ± SD	% RSD
1	50	31,85,876 ± 5840.40	0.18
2	75	49,85,081 ± 5706.74	0.11
3	100	65,71,087 ± 58055.84	0.89
4	125	81,17,682 ± 5634.22	0.07
5	150	98,20,802 ± 23296.13	0.24

Linear regression equation: $y = 65610x - 24876$
Correlation coefficient (R^2): 0.9993

Table 2: Linearity Data of POL

S. No.	Concentration (µg/mL)	Mean Area ± SD	% RSD
1	10	3,72,864 ± 907.01	0.24
2	15	5,60,642 ± 5773.50	1.04
3	20	7,18,915 ± 412.84	0.06
4	25	9,10,260 ± 414.04	0.05
5	30	10,74,314 ± 2966.33	0.28

Linear regression equation: $y = 35050x + 26392$

Correlation coefficient (R^2): 0.9992

2.3 Precision

Repeatability of the developed HPLC method was evaluated by analyzing samples at 650 µg/mL for Paracetamol (PCM) and 4 µg/mL for Polmacoxib (POL) using six replicate injections under the same conditions. The %RSD of the responses was found to be less than 2% for both analytes, indicating good precision and demonstrating that the method is repeatable.

Table 3: Repeatability Data for PCM and POL

S. No.	PCM Area (650 µg/mL)	POL Area (4 µg/mL)
1	6471014	718123
2	6571234	718925
3	6571902	718354
4	6572345	711980
5	6573245	713245
Mean	6551948	716125.4
SD	45249.38	3250.99
% RSD	0.69	0.45

2.3.1 Intraday Precision

The intra-day precision of the developed HPLC method was evaluated at 325, 650, and 975 µg/mL for Paracetamol (PCM) and 2, 4, and 6 µg/mL for Polmacoxib (POL). The analysis was performed in triplicate at different time intervals within a single day under identical chromatographic conditions. The %RSD values of peak areas were less than 2% at all levels, indicating acceptable precision and demonstrating the method's reproducibility and suitability for routine analytical applications.

Table 4: Data of Intraday for PCM

Concentration (µg. mL ⁻¹)	Intraday (Mean Area ± SD)	% RSD
325	3182757.3 ± 6204.21	0.19
650	6572497.3 ± 684.34	0.01
975	9829708 ± 8234.99	0.08

Table 5: Intraday Precision Data for POL

Concentration	Intraday	% RSD
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($\mu\text{g} \cdot \text{mL}^{-1}$)	(Mean Area $\pm$ SD)	
2	382003.67 $\pm$ 6964.47	1.82
4	714526.33 $\pm$ 3374.66	0.47
6	1059096.67 $\pm$ 18092.29	1.71

2.3.2 Inter-day precision : The inter-day precision of the developed HPLC method was evaluated at 325, 650, and 975 $\mu\text{g/mL}$ for Paracetamol (PCM) and 2, 4, and 6 $\mu\text{g/mL}$ for Polmacoxib (POL). The analysis was performed in triplicate over non-consecutive days under uniform chromatographic conditions. The %RSD values were found to be less than 2% at all levels, indicating acceptable precision and confirming the method's reproducibility and reliability for routine analysis.

Table 6: Inter-day Precision Data for PCM

Concentration ($\mu\text{g/mL}$)	Interday (Mean Area $\pm$ SD)	% RSD
325	3189120 $\pm$ 5764.85	0.18
650	6538498 $\pm$ 58451.22	0.89
975	9811417 $\pm$ 28290.56	0.29

2.4 Accuracy

The accuracy of the developed HPLC method was evaluated by recovery studies using the standard addition method at 80%, 100%, and 120% levels, each analyzed in triplicate. The percentage recovery for Paracetamol (PCM) and Polmacoxib (POL) was within 98–102% at all levels, indicating accuracy and absence of interference from excipients. The consistent recovery values demonstrate the reliability of the method for the determination of both analytes in the formulation.

Table 7: Inter-day Precision Data for POL

Concentration ($\mu\text{g/mL}$)	Interday (Mean Area $\pm$ SD)	% RSD
2	386613.67 $\pm$ 4690.06	1.21
4	718467.33 $\pm$ 412.84	0.06
6	1075568.33 $\pm$ 2966.33	0.28

Table 8a: Accuracy Data for PCM

Level of Spiking	Conc. of Formulation ($\mu\text{g/mL}$)	Amount Added ($\mu\text{g/mL}$)	Amount Recovered ($\mu\text{g/mL}$)	% Mean Recovery $\pm$ SD
Un-spiked	212	–	–	–
80%	212	487.5	487.52 $\pm$ 0.49	100.03 $\pm$ 0.65
100%	212	650	649.55 $\pm$ 0.53	99.55 $\pm$ 0.53
120%	212	812.5	812.18 $\pm$ 0.20	99.90 $\pm$ 0.16

Table 8b: Accuracy Data for POL

Level	Conc. of Formulation	Amount Added	Amount Recovered	% Mean Recovery
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of Spiking	($\mu\text{g/mL}$)	($\mu\text{g/mL}$)	($\mu\text{g/mL}$)	$\pm$ SD
Un-spiked	212	–	–	–
80%	212	3	3.05 $\pm$ 0.08	100.30 $\pm$ 0.53
100%	212	4	4.07 $\pm$ 0.10	100.34 $\pm$ 0.50
120%	212	5	5.02 $\pm$ 0.14	100.09 $\pm$ 0.55

2.5 Limit of Detection and Limit of Quantification

The LOD and LOQ were calculated on the basis of the formulae $\text{LOD} = 3.3 \times \sigma/S$ and $\text{LOQ} = 10 \times \sigma/S$, where σ is the standard deviation of the response and S is the slope of the calibration curve.

Table 9: LOD and LOQ Data for PCM and POL

Drug	LOD by Statistical Calculation ($\mu\text{g/mL}$)	LOQ by Statistical Calculation ($\mu\text{g/mL}$)
PCM	0.227	0.688
POL	0.335	1.015

2.6 Assay of Marketed Formulation

The developed RP-HPLC method was successfully applied to the assay of Paracetamol and Polmacoxib tablets. The assay values were found within acceptable limits (98–102%) with %RSD less than 2%, indicating that the method is accurate and precise for routine quality control analysis.

Table 10: Assay Result for PCM and POL

Drug	Amount taken ($\mu\text{g/mL}$)	Amount found ($\mu\text{g/mL}$) (Mean $\pm$ SD)	% Assay (Mean $\pm$ SD)
PCM	325	324.55 $\pm$ 0.53	99.55 $\pm$ 0.53
POL	2	2.07 $\pm$ 0.10	100.34 $\pm$ 0.50

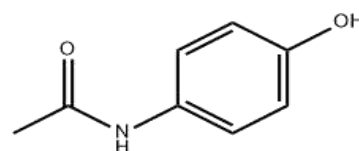


Fig. 1: Structure of Paracetamol

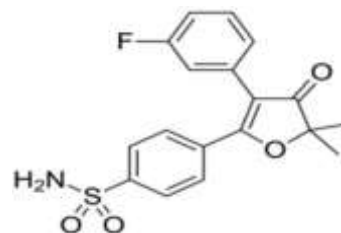


Fig. 2: Structure of Polmacoxib

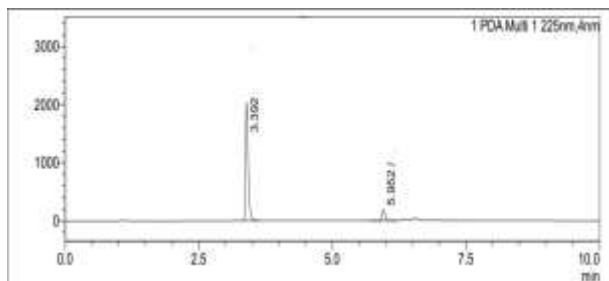


Fig. 3: Chromatogram of Optimized PCM and POL

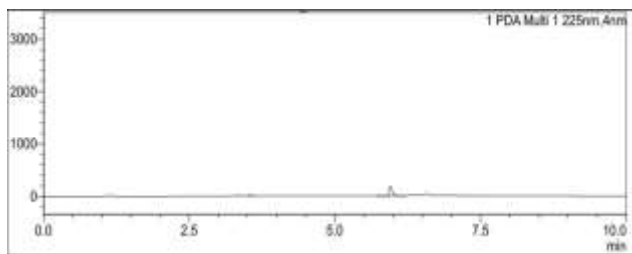


Fig. 4: Chromatogram of Polmacoxib

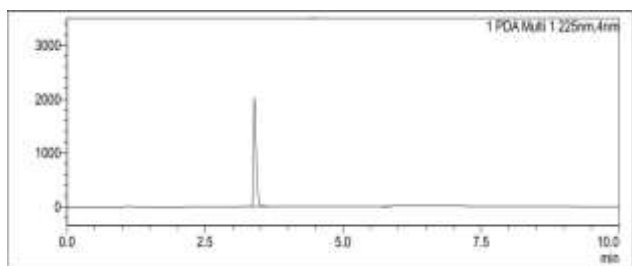


Fig. 5: Chromatogram of Paracetamol

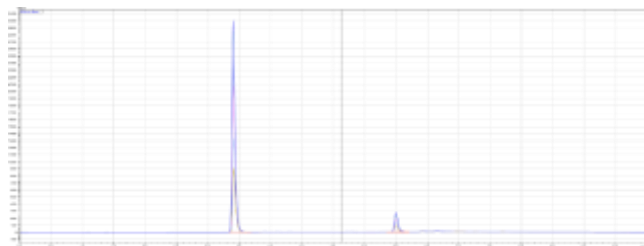


Fig. 6: Overlain Chromatograms for Linearity of PCM and POL

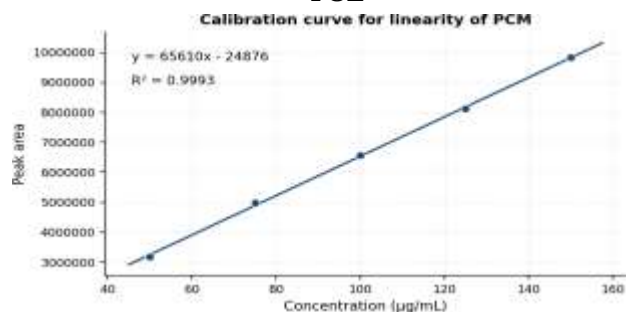


Fig. 7: Calibration Curve for Linearity of PCM

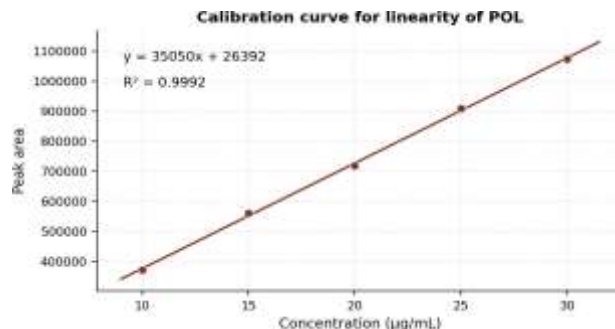


Fig. 8: Calibration Curve for Linearity of POL

Conclusion

RP-HPLC method was developed and validated for the simultaneous quantification of Paracetamol (PCM) and Polmacoxib (POL) in pharmaceutical dosage forms. The method showed good specificity with well-resolved peaks and no interference. Linearity exhibited a strong correlation between concentration and peak area, while precision studies showed

%RSD values within acceptable limits. Accuracy was confirmed through recovery studies within acceptance criteria, and the method was successfully applied to the assay of a marketed formulation. The proposed RP-HPLC method is therefore simple, rapid, accurate, and suitable for routine quality control analysis of Paracetamol and Polmacoxib in combined tablet dosage form.

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Conflict of Interest

The authors declare that there is no conflicts of interest related to this work.

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