



Development and Validation of a Novel UV-Spectrophotometric Method for Estimation of Piroxicam Using Hydrotropic Solvent in Bulk Drug and Pharmaceutical Dosage Form: A Research

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ABSTRACT:

A simple, rapid, accurate and economical UV-spectrophotometric method has been developed and validated for the estimation of Piroxicam in bulk drug and pharmaceutical tablet dosage form using 2% w/v sodium benzoate as hydrotropic solubilizing agent. Hydrotropic solubilization: A green and low-cost alternative for hazardous organic solvents used in spectrophotometric estimation of a poorly water soluble non-steroidal anti-inflammatory drug (NSAID) of oxamic acid class, Piroxicam. The absorption maximum (λ_{max}) of piroxicam was found to be 363nm in 2% sodium benzoate solution. Beer-Lambert's law was obeyed in the concentration range of 2–10 $\mu\text{g/mL}$. The method was validated for Accuracy, precision, linearity, range, intra-day and inter-day). The proposed method was successfully applied to the estimation of Piroxicam in marketed tablet formulations, and the percentage label claim was found to be within acceptable pharmacopoeial limits. The method eliminates the need for toxic organic solvents, is environmentally benign, and can be recommended for routine quality-control analysis of Piroxicam in bulk and dosage forms.

KEYWORDS: Piroxicam; UV-Spectrophotometry; Hydrotrophy; Sodium Benzoate; Method Validation; ICH Q2(R2); NSAID; Green Analytical Chemistry.

INTRODUCTION:

Piroxicam is a non-steroidal anti-inflammatory drug (NSAID) that belongs to the oxamic acid class of medications. It is chemically described as an enolic acid derivative of 4-hydroxy-2-methyl-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide. The main way it works is by inhibiting both COX-1 and COX-2 enzymes, which are responsible for producing prostaglandins. These substances are involved in causing inflammation, pain, and fever. Piroxicam is commonly used to treat the symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and other acute musculoskeletal conditions.

Piroxicam is recognized in several pharmacopoeias including the Indian Pharmacopoeia, British Pharmacopoeia, and United States Pharmacopoeia. These reference books recommend high performance liquid chromatography (HPLC) as the standard method for testing the purity of the drug. Although HPLC is highly accurate, it is often costly, requires specialized equipment and trained staff, and is time-consuming.

This makes it less suitable for routine quality control in areas with limited resources. As an alternative, UV-spectrophotometry is a quicker, less expensive, and more straightforward method for measuring the drug in both raw and prepared forms. However, this method is only effective when the drug is soluble in water or suitable solvents and has a chromophore that can absorb ultraviolet light.

Piroxicam is a nonsteroidal anti-inflammatory drug that is not very soluble in water. The use of UV-spectrophotometry to measure piroxicam typically involves organic solvents like methanol, ethanol, chloroform, dimethylformamide, and acetonitrile, or alkaline and buffered solutions. However, using organic solvents has several downsides, such as being environmentally harmful, expensive, and posing safety risks to lab workers. Because of these issues, there is increasing interest in developing more environmentally friendly analytical methods that reduce or eliminate the use of harmful solvents.

Hydrotropy is the process in which the solubility of a not-very-soluble substance in water is greatly enhanced by the presence of a second substance, called a hydrotrope. This happens without the formation of micelles or any change in the chemical structure of the drug. A number of hydrotropic agents like sodium benzoate, sodium salicylate, sodium citrate, sodium acetate, urea and nicotinamide have been used in literature for directly estimating the concentration of drugs using UV-spectrophotometry thus avoiding the use of toxic solvents. In this sodium benzoate has been successfully used for the improvement of solubility of various poorly water-soluble drugs. It is considered a safe, cheap and reliable alternative to conventional solvent systems.

The present work was planned to develop and validate simple, sensitive, accurate and low-cost UV-spectrophotometric method for estimation of piroxicam in bulk and commercial tablet preparations.

The hydrotropic agent employed in the method was 2% w/v solution of sodium benzoate. The method was fully validated as per International Council for Harmonisation (ICH) Q2(R2) guidelines.

ANALYSIS OF METHOD VALIDATION PARAMETERS:

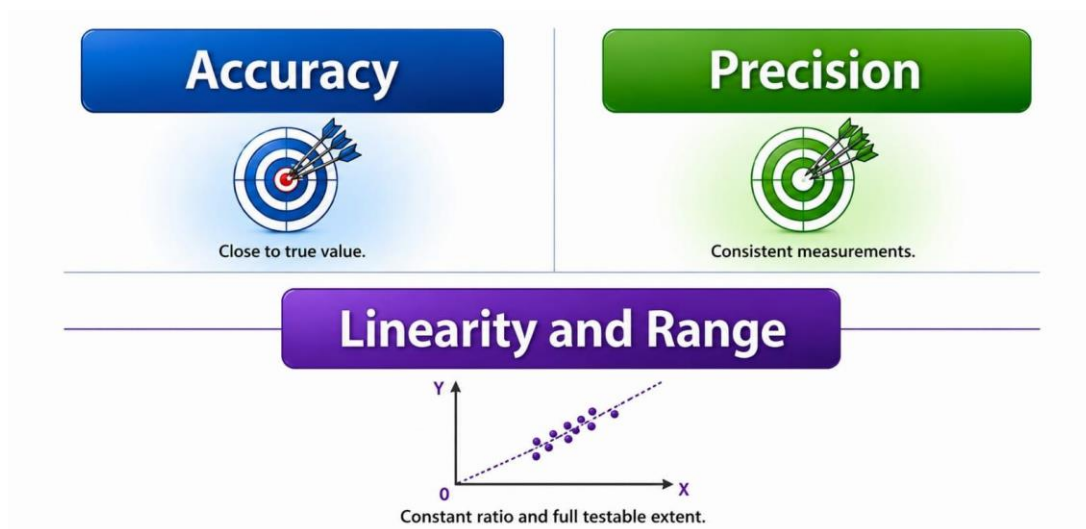


Figure 1: METHOD VALIDATION PARAMETERS:

1) ACCURACY

- ❖ Accuracy refers to how close the results obtained from an analytical method are to the accepted reference value.
- ❖ It can be assessed by comparing the recovery of the analyte or spiked samples with known concentrations.

2) PRECISION

- ❖ Precision is about how consistent the results are and is measured by the percent relative standard deviation from multiple samples.
- ❖ It should be evaluated at different levels according to ICH guidelines.

3) LINEARITY & RANGE

LINEARITY: The method's capability to generate results that are directly related to the amount of the substance being measured.

RANGE: The span between the highest and lowest levels of the substance that can be measured accurately, precisely, and consistently.

ASSAY IN UV SPECTROSCOPY

An assay in UV spectroscopy is used to find out the concentration of a specific substance.

TYPES OF ASSAYS

- 1. Quantitative assay:** This type of assay measures the exact amount of the substance present.
- 2. Limit test assay:** This assay checks whether the amount of the substance is within a specified range or limit.
- 3. Identification assay:** This assay is used to confirm whether a particular compound is present or not.

AIM:

Development and validation of a reliable, consistent, and cost-effective UV-spectrophotometric method for the determination of Piroxicam in both bulk drug and tablet dosage forms, utilizing 2% sodium benzoate as a hydrotropic solubilizing agent.

OBJECTIVES:

- To study the solubility enhancement of Piroxicam in 2% w/v sodium benzoate solution.
- The wavelength of maximum absorption (λ_{max}) of Piroxicam in 2% sodium benzoate solution was determined.
- To determine the linearity range and to prepare a calibration curve for Piroxicam Validation of the proposed method according to ICH Q2(R2) guidelines for accuracy, precision, linearity, and range
- To determine the percentage label claim and to apply the validated method for the estimation of Piroxicam in marketed tablet formulations.
- To illustrate the hydrotropic method as a safer, greener and economical alternative over conventional organic solvent-based methods

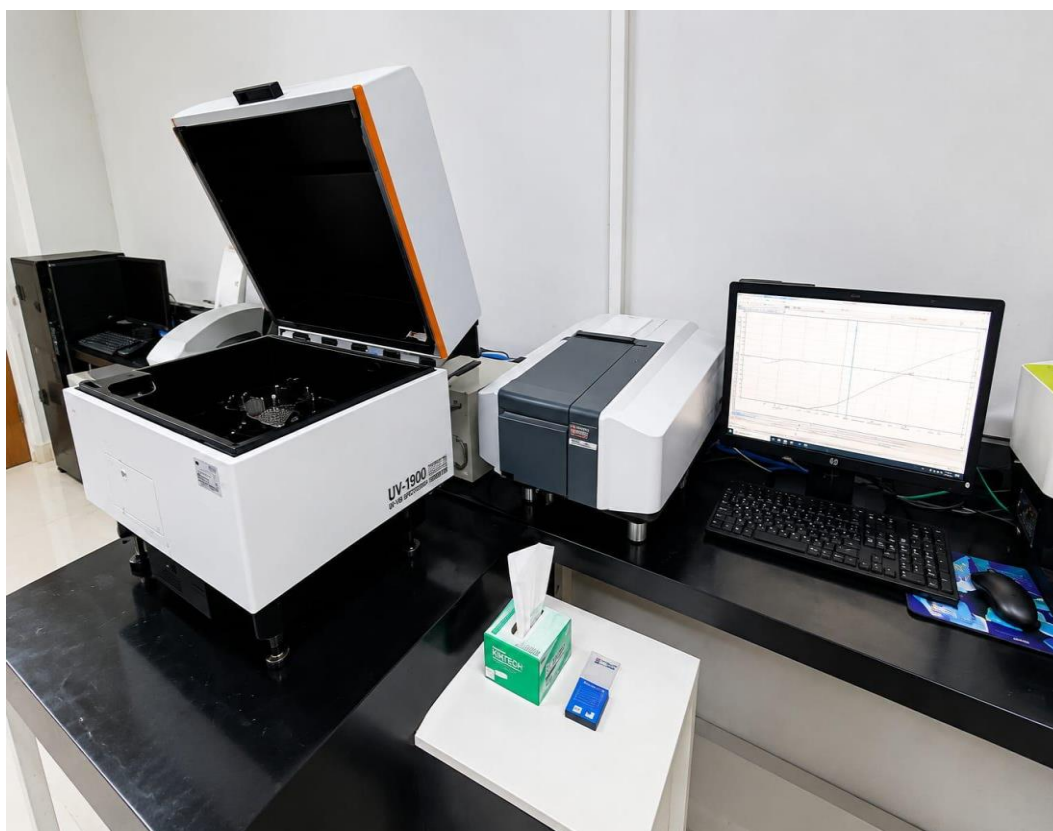


Figure 2: UV-Vis Spectrophotometer

PRINCIPLE OF UV SPECTROPHOTOMETRY:

UV-Vis spectrophotometry relies on the fact that molecules containing chromophoric groups absorb electromagnetic radiation in the ultraviolet (200–400 nm) or visible (400–800 nm) range promoting electrons from a ground state to an excited electronic state ($\pi \rightarrow \pi^*$ or $n \rightarrow \pi^*$ transitions). where A is absorbance, ϵ is the molar absorptivity ($\text{L mol}^{-1} \text{cm}^{-1}$), c is the molar concentration and l is the path length (cm) of the radiation through the sample. The Beer-Lambert law relates the absorption at a particular wavelength to the concentration of the absorbing species and the path length of the radiation through the sample. Piroxicam has a long-conjugated chromophore system consisting of benzothiazine and pyridyl rings that show characteristic UV absorption and are used for its spectrophotometric determination.

Ultraviolet-Visible Spectroscopy

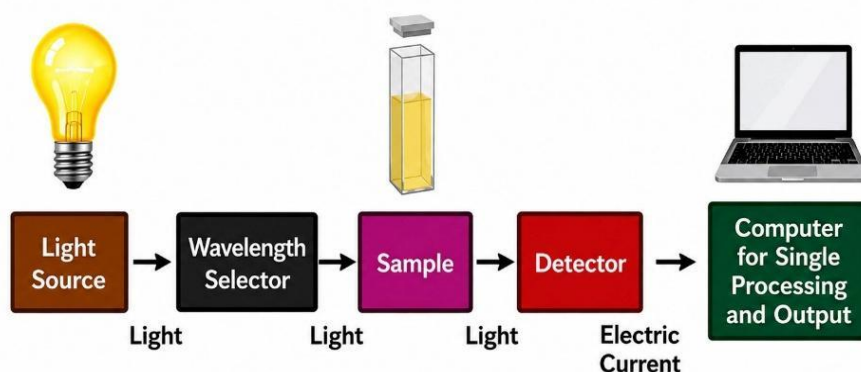


Figure 3: Schematic Diagram of the Working Principle of UV-Visible Spectroscopy

Light Spectrum

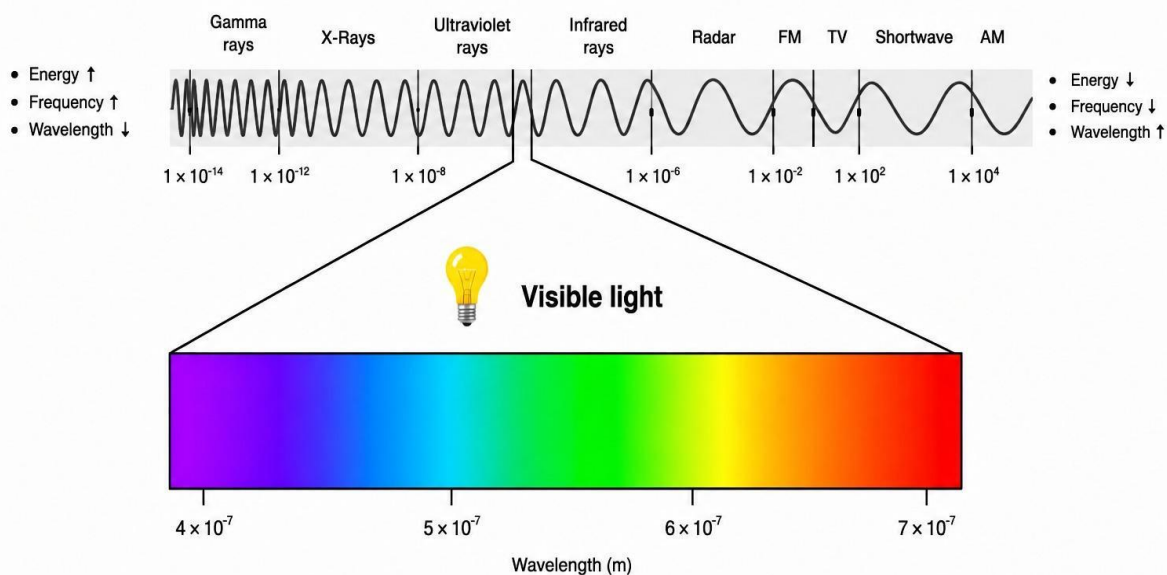


Figure 4: Electromagnetic Spectrum Highlighting the Ultraviolet and Visible Regions

HYDROTROPY AND SODIUM BENZOATE:

Hydrotropy is defined as a solubilization phenomenon whereby addition of a large quantity of a second solute (the hydrotropic agent) results in an increase in the aqueous solubility of another, poorly soluble solute. Unlike micellar solubilization by surfactants, hydrotropes do not possess a well-defined critical concentration or aggregation number, and the solubilizing action is generally attributed to the formation of soluble complexes or self-aggregation of the hydrotrope molecules that entrap the hydrophobic solute.

Commonly employed hydrotropic agents in pharmaceutical analysis include:

- Sodium benzoate
- Sodium citrate
- Sodium salicylate
- Sodium acetate
- Sodium ascorbate
- Urea
- Nicotinamide (niacinamide)

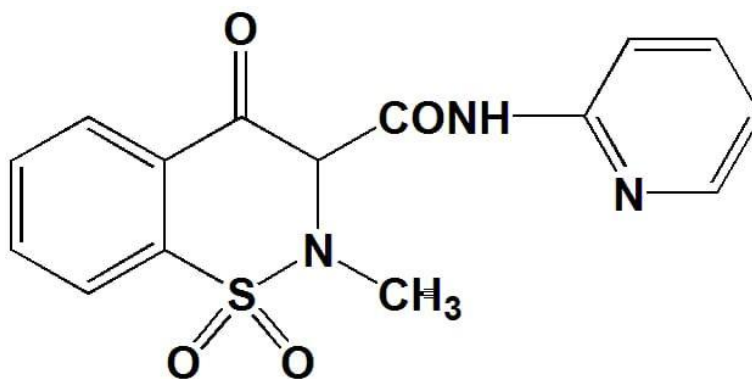
Sodium benzoate was selected as the hydrotropic agent in the present study owing to its high aqueous solubility, low cost, non-toxicity, lack of interference at the analytical wavelength of Piroxicam, and its established precedent in the hydrotropic estimation of other poorly water-soluble NSAIDs such as lornoxicam. A 2% w/v sodium benzoate solution was employed both for dissolution of the drug and as the diluent/blank throughout the study.

STRUCTURE, PROPERTIES, AND PHARMACOLOGICAL PROFILE OF PIROXICAM

Chemical Structure:

Chemical name (IUPAC): 4-Hydroxy-2-methyl-N-(pyridin-2-yl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

Canonical SMILES: CN1C(=C(O)c2ccccc2S1(=O)=O)C(=O)Nc1ccccn1



Piroxicam

Figure 5: Chemical Structure of Piroxicam

Molecular Formula:

$C_{15}H_{13}N_3O_4S$

Molecular Weight

331.35 g/mol

Category

Non-steroidal anti-inflammatory drug (NSAID); Oxicam derivative; Analgesic, antipyretic, and anti-inflammatory agent.

MECHANISM OF ACTION:

Piroxicam inhibits cyclo-oxygenase (COX-1 and COX-2) enzymes non-selectively, which prevents the conversion of arachidonic acid to the prostaglandin endoperoxides (PGG₂/PGH₂), precursors of prostaglandins and thromboxanes. The analgesic, anti-inflammatory and antipyretic effects of the drug are caused by the decrease of prostaglandin synthesis at sites of inflammation. Piroxicam also inhibits the migration of polymorphonuclear leukocytes and the release of lysosomal enzymes, which also accounts for its anti-inflammatory activity.

MATERIALS AND METHODS:

S. No	Materials	Specification
1	Piroxicam (Raw material – API)	Pharmaceutical grade
2	Piroxicam tablets (Brand A, B, C, D)	Marketed formulations, (Label claim 20mg)-Dispersible tablets
3	Sodium benzoate	Analytical reagent (AR) grade
4	Distilled water	Freshly prepared

Table 1:materials required

S. No	Instruments
1	UV-Visible Double Beam Spectrophotometer with matched 1cm quartz cells
2	Digital analytical balance (0.1 mg sensitivity)
3	Volumetric flasks (10, 50, 100 ml)
4	Mortar and pestle

Table 2: INSTRUMENTS REQUIRED

CHEMICALS AND REAGENTS

- Piroxicam working standard
- Sodium benzoate (AR grade)
- Distilled water
- Marketed Piroxicam tablet formulations (four brands, coded Brand A, B, C, and D)

PREPARATION OF SOLUTIONS

PREPARATION OF 2% W/V SODIUM BENZOATE SOLUTION

The stock solution of 2% w/v sodium benzoate was prepared by accurately weighing 2.0 g of sodium benzoate and dissolving it in about 70 mL of distilled water in a 100 mL volumetric flask with the aid of sonication and then the volume was made up to 100 mL with distilled water. This solution was used as a solvent/diluent and as a blank in the whole study.

PREPARATION OF STANDARD STOCK SOLUTION

An accurately weighed quantity of Piroxicam working standard equivalent to 10 mg was transferred to a 100 mL volumetric flask, dissolved in a sufficient quantity of 2% sodium benzoate solution with sonication, and the volume made up to the mark with the same solvent to obtain a stock solution of 100 µg/mL.

PREPARATION OF WORKING STANDARD SOLUTION:

A volume of 1 mL of standard stock solution (100 µg/mL) was pipetted out and diluted to 10 mL with 2% sodium benzoate solution to get a working standard solution of 10 µg/mL and that was further diluted as per calibration standards.

DETERMINATION OF λ_{max} :

An adequate aliquot of the working standard solution was scanned in the UV region of 200-400 nm against blank of 2% sodium benzoate solution in the UV-Visible double beam spectrophotometer. The drug showed the maximum absorbance at $\lambda_{\text{max}} = 363 \text{ nm}$ which was selected as the wavelength for further study.

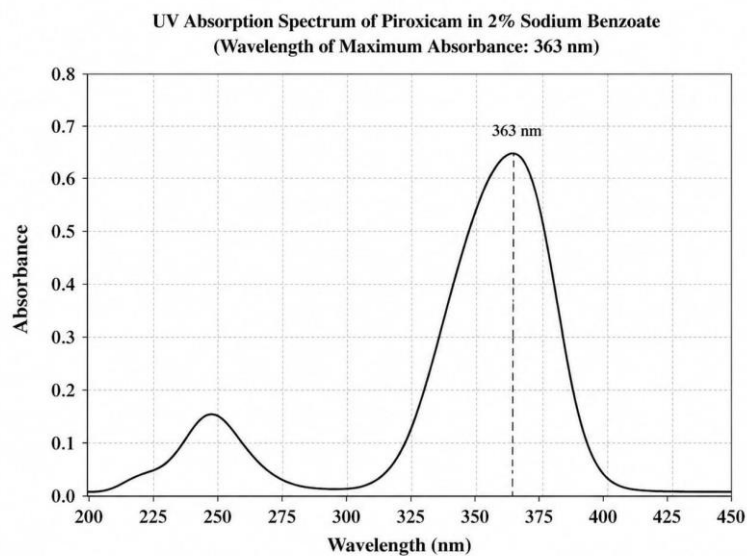


Figure 6: UV Absorption Spectrum of Piroxicam in 2% Sodium Benzoate

PREPARATION OF CALIBRATION STANDARDS

The working standard solution (10 µg/mL) was aliquoted out (0.2, 0.4, 0.6, 0.8 and 1.0 mL) and transferred into a series of 10 mL volumetric flasks and made up to the mark with 2% sodium benzoate solution to give final concentrations of 2, 4, 6, 8 and 10 µg/mL, respectively. The absorbance of each solution was measured against the blank at the λ_{max} .

BEER-LAMBERT LAW:

The amount of light that a solution absorbs is directly related to the amount of the substance that absorbs light and the distance that the light travels through the solution. This is what the Beer-Lambert Law says: ($A = \epsilon \cdot c \cdot l$)

It was found that Piroxicam follows the Beer-Lambert Law when the concentration of Piroxicam is between 2 and 10 micrograms per milliliter, in a solution that contains 2 percent Sodium benzoate

CALIBRATION CURVE:

S. No	Concentration (µg/ml)	Absorbance
1	2	0.232
2	4	0.363
3	6	0.461
4	8	1.051
5	10	1.169

Table 3: Calibration Data for Piroxicam in 2% Sodium Benzoate

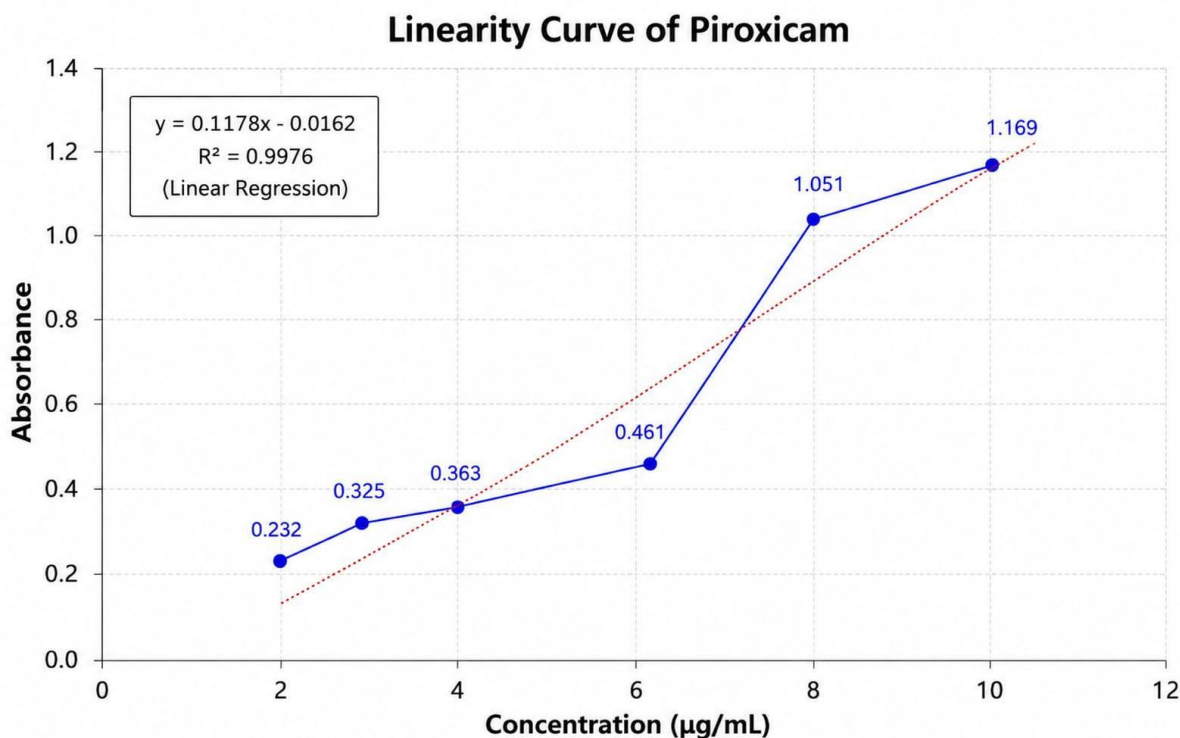


Figure 7: Linearity curve of piroxicam

S. NO	Volume of AML stock solution (ml)	Concentration of AML in final solution (µg/ml)	Absorbance at 363nm
1	0.2ml	2 µg/ml	0.232nm
2	0.3ml	2.5 µg/ml	0.325nm
3	0.4ml	4 µg/ml	0.363nm
4	0.6ml	6 µg/ml	0.461nm
5	0.8ml	8 µg/ml	1.051nm
6	1ml	10 µg/ml	1.169nm

Table 4: Concentration and Absorbance of Piroxicam at 363 nm

METHOD VALIDATION:

- The method that was developed was checked to make sure it works properly following the rules set by the International Council for Harmonisation also known as ICH Q2(R2) guidelines.
- These guidelines were used to check the Method Validation for things like how it works for different amounts, how accurate the Method Validation is and how precise the Method Validation is when it is repeated on the same day and on different days.
- The Method Validation was also checked for the amount that it can detect which is called the limit of detection and the smallest amount that it can measure which is called the limit of quantification.
- The Method Validation was also tested to see if it still works well even if some things are changed, which is called robustness and if it still works well when used by people or, in different places, which is called ruggedness.

ACCURACY

Accuracy is the closeness of the measured value to the true or accepted value.

It indicates how correctly the analytical method measures the actual amount of drug.

Accuracy is commonly expressed as percentage recovery (%)

REPLICATE	ABSORBANCE	CONCENTRATION	%RECOVERY
1	0.883	9.470	99.00
2	0.888	9.521	99.73
3	0.891	9.553	99.65

Table 5: ACCURACY AT 80% LEVEL

REPLICATE	ABSORBANCE	CONCENTRATION	% RECOVERY
1	1.083	11.540	99.00
2	1.081	11.520	99.00
3	1.086	11.571	100.00

Table 6: ACCURACY AT 100% LEVEL

REPLICATE	ABSORBANCE	CONCENTRATION	% RECOVERY
1	1.271	13.430	99.00
2	1.275	13.470	99.75
3	1.282	13.541	99.75

Table 7: ACCURACY AT 120% LEVEL

REPEATABILITY:

repeatability (method precision) was determined by measuring the absorbance of the same concentration solution six times under identical operating conditions on the same day.

Data for Repeatability:

Concentration (µg/ml)	Absorbance At 363nm	Mean value	Standard deviation	Standard error	Coefficient of variation
2	0.1768nm 0.1759nm 0.1728nm 0.1718nm	0.1743	0.0024	0.0012	1.3778
4	0.3266nm 0.3273nm 0.3285nm 0.3286nm	0.3278	0.0010	0.0005	0.2953
6	0.4913nm 0.4918nm 0.4917nm 0.4919nm	0.4917	0.0003	0.0001	0.0535
8	0.6342nm 0.6344nm 0.6348nm 0.6345nm	0.6345	0.0003	0.0001	0.0394

Table 8: Data for Repeatability

PRECISION

Precision was evaluated at three levels: repeatability, intraday precision, and interday precision, and expressed as % relative standard deviation (%RSD) of the absorbance/concentration values.

INTRADAY PRECISION

The intra-day precision was determined by analysis of three concentrations (10, 15 and 20 µg/mL) in triplicate on the same day.

S. No	Concentration in µg/ml	Absorbance at 363nm			RSD
		0hrs	1.5hrs	3hrs	
1	2	0.1656	0.1722	0.1426	9.7036
2	4	0.3245	0.3211	0.2993	4.3414
3	6	0.4855	0.4764	0.4596	2.7730
4	8	0.6236	0.6162	0.6052	1.5054

Table 9: INTRADAY PRECISION

INTERDAY PRECISION:

Interday precision was determined by analyzing the same three concentrations on three different days (Day 1, Day 2 and Day 3).

S. No	Concentration in µg/ml	Day 1	Day 2	Day 3	RSD%
1	2	0.1442	0.0877	0.1210	24.1429
2	4	0.2884	0.2213	0.3082	16.7056
3	6	0.4522	0.5490	0.4622	10.9135
4	8	0.6079	0.4168	0.5760	19.1866

Table 10: INTERDAY PRECISION

RESULT OF VALIDATION:**MARKETED TABLET FORMULATIONS**

Brand	Concentration µg/ml	Absorbance at 363nm	% Label Claim	Active content Per Tablet mg	Mean% Label Claim	Standard Deviation	Standard Error
Brand A	2	0.0886	38.91	7.78	34.74	5.9026	4.173
	4	0.1409	30.56	6.11			
Brand B	2	0.0820	36.11	7.22	34.09	2.8537	2.017
	4	0.1480	32.07	6.41			
Brand C	2	0.0920	40.36	8.07	37.49	4.0552	2.867
	4	0.1600	34.62	6.92			
Brand D	2	0.0820	36.11	7.22	33.25	4.0402	2.856
	4	0.1401	30.40	6.08			

Table 11: marketed formulation validation data

LINEARITY AND RANGE:

Linearity was assessed by creating a graph that shows the relationship between absorbance and concentration across the range of 2–10 µg/mL.

The correlation coefficient (r^2), slope, and intercept were calculated using the least-squares linear regression method. $r^2 = 0.9976$ regression equation: $Y = mX + c$.] The method's range refers to the concentration interval of the analyte in the sample where acceptable linearity, accuracy, and precision have been confirmed, which in this case is 2–10 $\mu\text{g/mL}$.

ASSAY PROCEDURE FOR MARKETED TABLET FORMULATIONS :

Tablets of each brand were accurately weighed and powdered finely. The quantity of powder equal to 100mg of Piroxicam was accurately weighed and transferred into a 100 mL volumetric flask and dissolved in an adequate amount of 2% sodium benzoate solution with sonication for 20 minutes and filtered through Whatman filter paper No.1 and volume was made up to the mark with the same solvent. Aliquots were suitably diluted with 2% sodium benzoate solution to be within the linearity range and the absorbance was measured at the selected λ_{max} against blank. The above was repeated for the three commercial brands (Brand A, Brand B, Brand C and Brand D).

ASSAY CALCULATION

BRAND: A

- ❖ Weight of 6 tablets: 1.962g (Average weight = 0.327g).
- ❖ Weight to be taken: $0.327\text{g}/0.02 \times 0.1 = 1.635\text{g}$.
- ❖ Absorbance: Sample 0.231, $A1\%1\text{cm} = 1160\text{nm}$.

S. No	Content	Absorbance
1	$A1\%1\text{cm}$	1160nm
2	Sample	0.231
3	Blank	0

Table 12: brand A assay

Concentration of piroxicam: 0.0995gms.

Amount of piroxicam: $0.0995 \times 0.327 / 1.635 = 0.0199\text{gms}$.

Percentage Purity: $(0.0199/0.02 \times 100) = 99.50\%$

BRAND: B

- ❖ Weight of 6 tablets: 1.386g (Average weight = 0.231)
- ❖ Weight to be taken: $0.231/0.02 \times 0.1 = 1.155\text{g}$
- ❖ Absorbance: Sample 0.229, $A1\%1\text{cm} = 1160\text{nm}$

S. No	Content	Absorbance
1	$A1\%1\text{cm}$	1160
2	sample	0.229
3	Blank	0

Table 13: brand B assay

Concentration of piroxicam: 0.0985gms

Amount of piroxicam: $0.0985 \times 0.231 / 1.155 = 0.0197$

Percentage Purity: $(0.0197/0.02 \times 100) = 98.5\%$

BRAND: C

- ❖ Weight of 6 tablets: 2.348g (Average weight = 0.391g).
- ❖ Weight to be taken: $0.391\text{g}/0.02 \times 0.1 = 1.955\text{g}$.
- ❖ Absorbance: Sample 0.230, $A1\%1\text{cm} = 1160\text{nm}$

S.NO	Content	Absorbance
1	A1%1cm	1160
2	Sample	0.230
3	Blank	0

Table 14: brand C assay

Concentration of piroxicam: 0.099gms

Amount of piroxicam: $0.099 \times 0.391 / 1.955 = 0.0198$

Percentage Purity: $(0.0198 / 0.02 \times 100) = 99\%$

BRAND: D

- ❖ Weight of 6 tablets: 0.915g (Average weight = 0.1525g).
- ❖ Weight to be taken: $0.1525g / 0.02 \times 0.1 = 0.7625g$.
- ❖ Absorbance: Sample 0.227, A1%1cm = 1160nm

S.NO	Content	Absorbance
1	A1% 1cm	1160
2	Sample	0.227
3	Blank	0

Table 15: brand D assay

Concentration of piroxicam: 0.0975gms

Amount of piroxicam: $0.0975 \times 0.1525 / 0.7625 = 0.0195$

Percentage Purity: $(0.0195 / 0.02 \times 100) = 97.50\%$

RESULTS:

S. No	Various Brands	Absorbance	%Purity
1	Brand A	0.231nm	99.50%
2	Brand B	0.229nm	98.50%
3	Brand C	0.230nm	99.00%
4	Brand D	0.227nm	97.50%

Table 16: Brand comparison assay result

DISCUSSION:

A simple, sensitive and economical alternative to the conventional organic-solvent based or chromatographic methods for the estimation of Piroxicam has been proposed by using 2% sodium benzoate as hydrotropic solubilizing agent in UV-spectrophotometric method. The method overcomes the limitations of organic solvents such as toxicity, high cost and environmental hazard while providing comparable accuracy and precision. The validation data obtained met acceptance criteria as outlined in ICH Q2 (R2) and confirmed the suitability of the method for routine quality-control analysis. The small variation in percentage label claim among the three marketed brands can be due to variation in the manufacturing processes, excipient composition, or formulation technology among manufacturers.

CONCLUSION:

A simple, accurate, precise and economical UV-spectrophotometric method using 2% sodium benzoate as a green hydrotropic solubilizing agent was successfully developed and validated for estimation of Piroxicam in bulk drug and marketed tablet formulations as per ICH Q2(R2) guidelines. The method showed good linearity, accuracy, precision, robustness and ruggedness and can be recommended as a suitable, environmentally friendly alternative for routine quality-control analysis of Piroxicam removing the requirement of hazardous organic solvents.

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AUTHOR CONTRIBUTION:

Pragadheswaran S, Pramila L, Pravin kumar M, Priyan S had principal responsibility for the conception, design of the study and drafting of manuscript. Ramanathan.N was responsible for the revision of the manuscript for important intellectual content, Dr. J. Karthi, Dr. S. Swarnalatha contributed towards reviewing of the literature.

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