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DETERMINATION OF FLURBIPROFEN IN PHARMACEUTICAL PREPARATIONS BY FIRST-ORDER DERIVATIVE SPECTROPHOTOMETRY METHOD

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Keywords:

Flurbiprofen, First-order derivative spectrophotometry, Validation, Pharmaceutical preparation

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ABSTRACT: Flurbiprofen is a new non-steroidal anti-inflammatory agent, one of the propionic acid groups, which has significant anti-inflammatory, analgesic, and antipyretic properties. Clinically, it is used for the treatment of rheumatoid arthritis, degenerative joint disease, osteoarthritis, ankylosing spondylitis, acute musculoskeletal disorders, low back pain, and allied conditions. In this study, the first-order derivative spectrophotometry method was developed for the determination of flurbiprofen in pharmaceutical preparations. In the first derivative spectrophotometry, absorbance values were measured at 213, 233 and 260 nm. Parameters such as linearity, precision, accuracy, specificity, stability, limit of detection and limit of quantitation were studied according to the International Conference on Harmonization Guidelines. A calibration curve was linear between the concentration ranges of 1-14 μg ml^{-1}. Within- and between-day precision values for flurbiprofen were less than 4.95%, and accuracy (relative error) was better than 3.67%. The mean recovery value of flurbiprofen was 100.9% for pharmaceutical preparations. The developed method was successfully applied to tablet formulations and the results were compared statistically with each other.

INTRODUCTION: Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed agents worldwide to treat a variety of pain-related conditions, including arthritis and other rheumatic diseases. Also, epidemiological studies have shown that long-term use of NSAIDs reduces the risk of developing Alzheimer's disease and delays its onset [1-3]. Flurbiprofen **Fig. 1** is used for the treatment of rheumatoid arthritis, degenerative joint disease, osteoarthritis, unclosing spondylitis, acute musculo-skeletal disorders, low back pain, and allied conditions [4-7].

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It contains a fluorine atom in its molecular structure, producing better effects at a lower therapeutic dose and with less adverse effects compared with similar drugs.

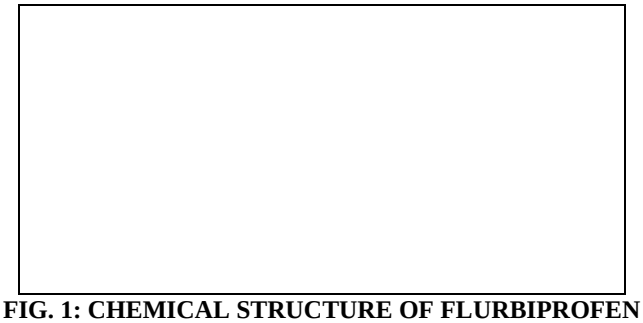

FIG. 1: CHEMICAL STRUCTURE OF FLURBIPROFEN

Several methods have been reported for the determination of flurbiprofen including High-Performance Liquid Chromatography (HPLC) [8-19] and Liquid Chromatography-Mass Spectrometry (LC-MS) [20]. Over the last 20 years, several HPLC methods using UV or fluorescence detection have

been reported for the estimation of flurbiprofen either alone or together with their metabolites in plasma/serum [8-13], in urine [14-18] and ocular fluids [19]. USP 2000 [21] and BP 1993 [22] both have recommended HPLC method for analysis of pure flurbiprofen and in dosage form (tablet and ophthalmic drops). Both the methods recommended the use of a mobile phase of acetonitrile-water-glacial acetic acid (60:35:5) at a flow rate of 1 mL/min. IP 1996 [23] has suggested a titrimetric method for flurbiprofen estimation.

However, to our knowledge, there is no individual first-order derivative spectrophotometric method for the determination of flurbiprofen in pharmaceutical preparations in literature. Derivative spectrophotometry is an analytical technique of great utility for extracting both qualitative and quantitative information from spectra composed of unresolved bands, and for eliminating the effect of baseline shifts and baseline tilts. It consists of calculating and plotting one of the mathematical derivatives of a spectral curve [24]. Last year, this technique rapidly gained ground in the application in the analysis of pharmaceutical preparations.

We wanted to develop a new spectrophotometric method for the determination of flurbiprofen in pharmaceutical preparations without the necessity of sample pre-treatment. After developing the first-order derivative spectrophotometric method was also carried out and all optimization parameters were also considered. Also, the developed methods were applied to commercial preparations (Majezik, Frolix, Maximus, Zero-P, and Fortune) as a tablet. The results obtained were statistically compared.

MATERIALS AND METHODS:

Chemicals: Flurbiprofen was obtained from Sigma (St. Louis, MO, USA). Majeski, Frolix, Maximus, Zero-P and Fortune tablets (100 mg flurbiprofen) were obtained the pharmacy (Erzurum, Turkey).

Instrument: A Thermospectronic double-beam UV - Visible spectrophotometer (HEλIOSβ, Thermo Spectronic, Cambridge, UK) with the local control software was used. First-order derivative spectra of reference and sample solutions were recorded in 1cm quartz cells at a scan speed of 600 nm min^{-1}, a scan range of 190-320 nm and fixed slit width of 2 nm.

Preparations of the Standard and Quality Control Solutions: The stock standard solution of flurbiprofen was prepared in acetonitrile to a concentration of 100 µg ml^{-1} and kept stored at -20 °C in dark glass flasks. Working standard solutions were prepared from the stock standard solutions. A calibration graph was constructed in the range of 1, 2, 4, 6, 8, 10, 12 and 14 µg ml^{-1} for flurbiprofen (n=6). For quality control samples containing concentration 3, 9 and 13 µg ml^{-1} of flurbiprofen, the stock solution was diluted with acetonitrile.

Assay Sample Preparation: The average capsule mass was calculated from the mass of tablets of Majezik, Frolix, Maximus, Zero-P, and Fortune (100 mg flurbiprofen tablet, which was composed of flurbiprofen and some excipients). They were then finely ground, homogenized and a portion of the powder was weighed accurately, transferred into a 100 mL brown measuring flask and diluted to scale with acetonitrile. The mixture was sonicated for at least 10 min to aid dissolution and then filtered through a Whatman 42 paper. An appropriate volume of filtrate was diluted further with acetonitrile so that the concentration of flurbiprofen in the final solution was within the working range and then recorded against acetonitrile.

Data analysis: All statistical calculations were performed with the Statistical Product and Service Solutions (SPSS) for Windows, version 10.0. Correlations were considered statistically significant if calculated P values were 0.05 or less.

RESULTS AND DISCUSSION:

Method Development: The derivative wavelength difference (Δλ) n values (smoothing factor). Generally, the noise decreases by increasing. Optimal wavelength range should be chosen since the broad peaks become sharper, the ratio of signal/noise elevates, and the sensitivity of the method increases by controlling the degree of low pass filtering or smoothing. Therefore, a series of n values (n=1-9) were tested in the first-order derivative spectra of flurbiprofen in acetonitrile. Optimum results were obtained in the measuring wavelength range 190-320 nm, n=5 (Δλ=17.5 nm) for the first-order derivative spectrophotometric method.

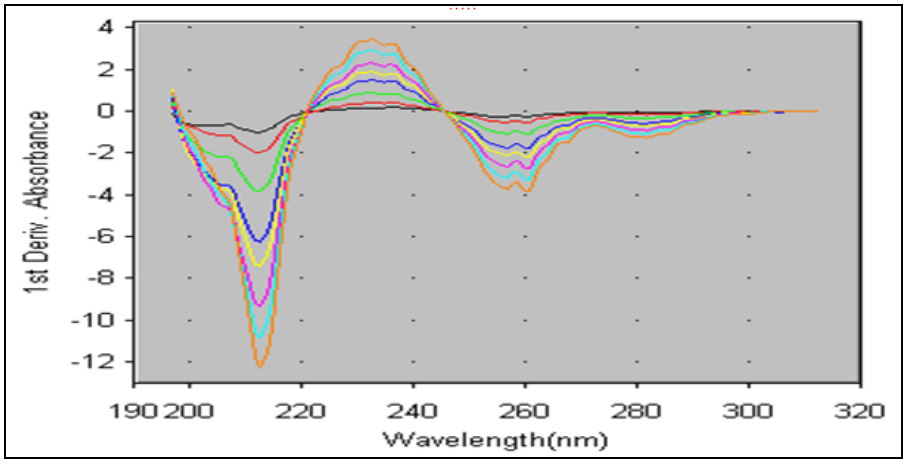

FIG. 2: FIRST-ORDER DERIVATIVE SPECTRUMS OF STANDARD SOLUTIONS OF FLURBIPROFEN

Fig. 2 presents the overlay of first-order ultraviolet spectra of standard flurbiprofen samples in acetonitrile. As demonstrated in **Fig. 2**, the maximum peak is represented at 233, and minima peaks are shown at 213 and 260 nm. As no difference was observed between the spectra of flurbiprofen standard and tablet solutions and in the maximum and minima wavelengths of all spectra, it was suggested that the developed methods allowed complete elimination of the background absorption due to the tablet excipients at the chosen wavelengths both in first-order derivative spectra of flurbiprofen.

Method Validation:

Linearity: For quantitative analysis of flurbiprofen, the calibration curves were plotted for each spectrophotometric method over the concentration ranges cited. The peak to zero methods for calibration curve in the first-order derivative spectrophotometric method was used. The linearity ranges of all spectrophotometric method were found to be 1-14 µg ml^{-1}. The statistical parameters and regression equations which were calculated from the calibration curves along with the standard error of the slope and the intercept are given in **Table 1**.

TABLE 1: RESULTS OF REGRESSION ANALYSIS OF FLURBIPROFEN

Wavelength λ: nm	213	233	260
Linearity µg ml^{-1}	1-14	1-14	1-14
Linear regression	D_1=0.8725x+0.3947	D_1=0.2547x-0.1097	D_1=0.2754x+0.0104
S_a	2.68×10^{-2}	3.18×10^{-2}	3.74×10^{-2}
S_b	5.62×10^{-3}	7.98×10^{-3}	6.26×10^{-3}
Coefficient of correlation (r)	0.9948	0.9973	0.9981
S_r	4.65×10^{-3}	3.76×10^{-3}	2.87×10^{-3}

S_a: Standard deviation of intercept of the regression line, S_b: Standard deviation of the slope of the regression line, S_r: Standard deviation of coefficient of correlation.

Limits of Detection (LOD) and Quantitation (LOQ): The LOD and LOQ of flurbiprofen by the proposed methods were determined using calibration standards. LOD and LOQ values were calculated as 3.3 σ/S, and 10 σ/S, respectively, where S is the slope of the calibration curve and σ is the standard deviation of y-intercept of regression equation (n=6) [25] **Table 1**.

Specificity: Comparison of the first-order derivative spectrum of flurbiprofen in standard and drug formulation (Majezik, Frolix, Maximus, Zero-P and Fortine tablet) solutions show that the wavelengths of maximum and minimum absorbance do not change **Fig. 3**. According to the results obtained, the first-order the derivative spectrophotometric method can access the flurbiprofen in the presence of excipients, and hence, the method can be considered specific.

Accuracy and Precision: The precision of the analytic method was determined by repeatability (within-day) and intermediate precision (between-day). Three different concentrations which were quality control samples (3, 9, 13 µgml^{-1}) were analyzed six times per day for within-day precision

and once daily for three days for between-day precision. Repeatability was ≤3.10% (n=6) and intermediate precision was ≤4.95%, (n=6), respectively **Table 2**.

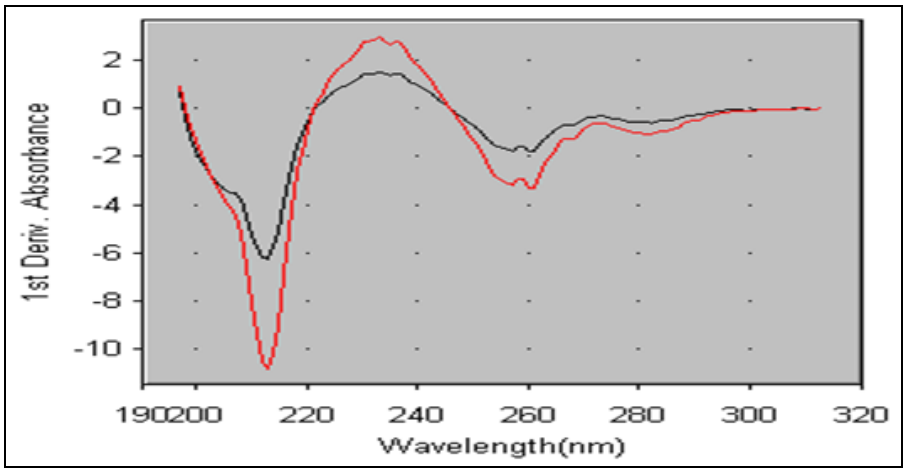

FIG. 3: FIRST-ORDER DERIVATIVE SPECTRUMS OF MAJEZIK TABLET SOLUTIONS CONTAINING FLURBIPROFEN

TABLE 2: PRECISION AND ACCURACY OF FLURBIPROFEN

		Within-day			Between-day		
Method	**Added (µg ml^{-1})**	**Found (µg ml^{-1}) X±SD**	**Accuracy**	**Precision RSD%[a]**	**Found (µg ml^{-1}) X±SD**	**Accuracy**	**Precision RSD%[a]**
1 $D_{213\ nm}$	3	3.07±0.038	2.33	1.24	3.09±0.075	3.00	2.43
1 $D_{233\ nm}$	3	3.06±0.048	2.00	1.57	3.07±0.085	2.33	2.77
1 $D_{260\ nm}$	3	2.95 ± 0.081	-1.67	2.75	3.11±0.154	3.67	4.95
1 $D_{213\ nm}$	9	9.11±0.198	1.22	2.17	9.16±0.281	1.78	3.07
1 $D_{233\ nm}$	9	9.02±0.192	0.22	2.13	9.13±0.285	1.44	3.12
1 $D_{260\ nm}$	9	9.13±0.275	1.44	3.01	9.12±0.289	1.33	3.17
1 $D_{213\ nm}$	13	13.12±0.421	0.92	3.21	13.16±0.425	1.23	3.22
1 $D_{233\ nm}$	13	13.08±0.416	0.62	3.18	12.89±0.398	-0.84	3.09
1 $D_{260\ nm}$	13	12.85±0.472	-1.15	3.67	13.11±0.462	0.84	3.52

X: Mean, SD: Standard deviation of six replicate determinations, RSD: Relative standard derivation, [a]Average of six replicate determinations, Accuracy: (%relative error) (found-added)/added × 100

Recovery: To determine the accuracy of the first-order derivative spectrophotometric method and to study the interference of formulation additives, the recovery was checked at three different concentration levels (2, 6, 10 µg ml^{-1}) and analytical recovery experiments were performed by adding known amount of pure drugs to pre-analyzed samples of commercial dosage form (Majezik, Frolix, Maximus, Zero-P and Fortine tablet). The percent analytical recovery values were calculated by comparing concentration obtained from the spiked samples with actually added concentrations. The mean recovery of the first-order derivative spectrophotometric method was 100.9 **Table 3**.

Stability: To evaluate the stability of flurbiprofen, standard solutions were prepared separately at concentrations covering the low, medium and higher ranges of calibration curve for different temperature and times. These solutions were stored at room temperature, refrigerator (4 °C) and frozen (-20 °C) temperature for 24 h and 72h. The results were evaluated comparing these measurements with those of standards and expressed as percentage deviation and flurbiprofen was found as stable at room temperature, 4 and -20 °C for at least 72h **Table 4**.

Ruggedness: In this study, first-order derivative spectrophotometric determination of flurbiprofen was carried out by a different analyst in same instrument with the same standard **Table 5**. The result showed no statistical differences between different operators suggesting that the developed method was rugged.

TABLE 3: RECOVERY VALUES OF FLURBIPROFEN IN PHARMACEUTICAL PREPARATIONS

			Within-day			Between-day		
Commercial Preparation	**Method**	**Added (μg ml^{-1})**	**Found (μg ml^{-1}) X±SD**	**Recovery (%)**	**RSD %[a]**	**Found (μg ml^{-1}) X±SD**	**Recovery (%)**	**RSD %[a]**
Majezik (2 μg ml^{-1})	1 $D_{213\ nm}$	2	1.99±0.031	99.6	1.56	2.06±0.032	103.0	1.55
	1 $D_{233\ nm}$	2	1.97±0.025	98.5	1.27	2.04±0.041	102.0	2.01
	1 $D_{260\ nm}$	2	1.98±0.033	99.0	1.67	2.03±0.038	101.5	1.87
	1 $D_{213\ nm}$	6	5.97±0.146	99.4	2.45	6.08±0.142	101.3	2.34
	1 $D_{233\ nm}$	6	5.98±0.165	99.7	2.76	6.05±0.152	100.8	2.51
	1 $D_{260\ nm}$	6	6.09±0.178	101.5	2.97	5.97±0.171	99.5	2.86
	1 $D_{213\ nm}$	10	9.89±0.226	98.9	2.29	9.85±0.211	98.5	2.14
	1 $D_{233\ nm}$	10	9.85±0.211	98.5	2.14	10.18±0.147	101.8	1.44
	1 $D_{260\ nm}$	10	10.12±0.285	101.2	2.82	10.09±0.256	100.9	2.54
Frolix (2 μg ml^{-1})	1 $D_{213\ nm}$	2	1.96±0.038	97.7	1.94	1.99±0.019	99.5	0.95
	1 $D_{233\ nm}$	2	1.97±0.028	98.5	1.42	2.04±0.033	102.0	1.62
	1 $D_{260\ nm}$	2	2.03±0.067	101.6	3.30	2.03±0.042	101.5	2.07
	1 $D_{213\ nm}$	6	5.98±0.129	99.7	2.17	6.08±0.145	101.3	2.38
	1 $D_{233\ nm}$	6	5.92±0.132	98.7	2.22	5.96±0.150	99.3	2.52
	1 $D_{260\ nm}$	6	6.02±0.148	100.3	2.46	5.97±0.142	99.5	2.38
	1 $D_{213\ nm}$	10	10.08±0.276	100.8	2.74	9.98±0.263	99.8	2.64
	1 $D_{233\ nm}$	10	9.99±0.256	99.9	2.56	10.13±0.295	101.3	2.91
	1 $D_{260\ nm}$	10	9.94±0.194	99.4	1.95	9.97±0.242	99.7	2.43
Maximus (2 μg ml^{-1})	1 $D_{213\ nm}$	2	2.03±0.086	101.4	4.24	1.99±0.076	99.5	3.82
	1 $D_{233\ nm}$	2	1.98±0.058	99.0	2.93	1.97±0.062	98.5	3.14
	1 $D_{260\ nm}$	2	2.04±0.096	102.0	4.71	1.97±0.058	98.5	2.94
	1 $D_{213\ nm}$	6	5.98±0.253	99.7	4.23	5.98±0.149	99.7	2.49
	1 $D_{233\ nm}$	6	6.04±0.228	100.7	3.77	5.96±0.255	99.3	4.28
	1 $D_{260\ nm}$	6	5.92±0.142	98.7	2.39	5.96±0.142	99.3	2.38
	1 $D_{213\ nm}$	10	9.88±0.343	98.8	3.47	9.98±0.366	99.8	3.67
	1 $D_{233\ nm}$	10	9.98±0.262	99.8	2.63	10.08±0.288	100.8	2.86
	1 $D_{260\ nm}$	10	9.94±0.194	99.4	1.95	9.96±0.235	99.6	2.36
Zero-P (2 μg ml^{-1})	1 $D_{213\ nm}$	2	1.95±0.066	97.4	3.38	1.98±0.030	99.0	1.52
	1 $D_{233\ nm}$	2	2.02±0.031	101.0	1.53	2.03±0.038	101.5	1.87
	1 $D_{260\ nm}$	2	2.04±0.045	102.0	2.21	1.99±0.052	99.5	2.61
	1 $D_{213\ nm}$	6	5.91±0.146	98.7	2.22	6.02±0.150	99.3	2.52
	1 $D_{233\ nm}$	6	5.91±0.187	98.4	3.16	6.03±0.198	100.5	3.28
	1 $D_{260\ nm}$	6	5.95±0.201	99.2	3.38	6.05±0.210	100.8	3.47
	1 $D_{213\ nm}$	10	9.95±0.385	99.5	3.87	10.08±0.288	100.8	2.86
	1 $D_{233\ nm}$	10	10.05±0.244	100.5	2.43	10.09±0.285	100.9	2.82
	1 $D_{260\ nm}$	10	10.06±0.253	100.6	2.51	9.96±0.352	99.6	3.53
Fortine (2 μg ml^{-1})	1 $D_{213\ nm}$	2	2.02±0.043	101.0	2.13	2.03±0.078	101.4	3.84
	1 $D_{233\ nm}$	2	1.99±0.022	99.5	1.11	1.98±0.086	99.0	4.34
	1 $D_{260\ nm}$	2	2.04±0.035	102.0	1.72	2.04±0.092	102.0	4.51
	1 $D_{213\ nm}$	6	5.98±0.153	99.7	2.56	5.98±0.175	99.7	2.93
	1 $D_{233\ nm}$	6	5.96±0.268	99.3	4.49	6.05±0.169	100.8	2.79
	1 $D_{260\ nm}$	6	5.96±0.164	99.3	2.75	5.97±0.195	99.5	3.27
	1 $D_{213\ nm}$	10	10.22±0.198	102.2	1.94	9.85±0.252	98.5	2.56
	1 $D_{233\ nm}$	10	10.12±0.285	101.2	2.82	10.18±0.162	101.8	1.59
	1 $D_{260\ nm}$	10	9.98±0.268	99.8	2.69	10.09±0.296	100.9	2.93

X: Mean, SD: Standard deviation of six replicate determinations, RSD: Relative standard derivation.
[a]Average of six replicate determinations.

TABLE 4: STABILITY OF FLURBIPROFEN IN SOLUTION

Method	Added (μg ml^{-1})	Room temperature stability 24 h	Room temperature stability 72 h	Refrigeratory stability, +4°C 72 h	Frozen stability, -20 °C 72 h
1 $D_{233\ nm}$	5	102.9±0.064	98.76±3.216	100.1±1.020	98.70±0.264
	10	98.09±4.507	100.8±2.034	99.30±0.094	98.57±0.214
	15	103.0±1.228	99.18±1.234	103.7±0.076	101.5±0.096

[a]Recovery % of of six replicate determinations

TABLE 5: THE RESULTS OF ANALYSES OF FLURBIPROFEN BY A DIFFERENT ANALYST[a]

Method	λ (nm)	Added (μg ml^{-1})	Found (μg ml^{-1}) X±SD	Recovery (%)	RSD (%)
First-order Spectrophotometric Method	$1D_{233\ nm}$	5	4.89±0.138	98.4	2.96
		10	10.14±0.421	101.7	2.89
		15	15.18±0.541	100.9	1.91

λ: Wavelength (nm), X: Mean, Mean measurements of six replicate determinations

Comparıson of the Methods: Flurbiprofen is a non-steroidal anti-inflammatory agent, one of the propionic acid groups, which has significant anti-inflammatory, analgesic, and antipyretic properties. In this study, a fast and simple first-order derivative spectrophotometric method is employed in the analysis of commercial preparations in the drug industry. The proposed method is used so much because it is a method easy to apply.

Also, Pharmacopoeias [21-23] have reported titrimetric and liquid chromatographic methods for the analysis of flurbiprofen in pure form and pharmaceutical formulations. Titrimetric method involves dissolving about 0.5 g of accurately weighed flurbiprofen in 100 mL of alcohol (previously neutralized with 0.1M sodium hydroxide versus to the phenolphthalein end point) and then, titrating the same (after adding phenolphthalein) with 0.1M sodium hydroxide versus till the first appearance of faint pink colour that persists for not less than 30 sec. Each ml of 0.1 M sodium hydroxide is equivalent to 24.43 mg of flurbiprofen. Another method has recommended liquid chromatographic (HPLC) method for analysis of related substances in pure flurbiprofen and assay of flurbiprofen in pharmaceutical dosage form (tablet and ophthalmic drop). The methods recommended using a mobile phase of water-acetonitrile-glacial acetic acid (60:35:5, v/v) at a flow rate of 1 mL min^{-1}, using UV detection (254 nm) on a stainless steel column (4 μm, 3.9×15 cm i.d.). A first-order derivative spectrophotometric method was applied for the determination of the commercial tablets **Table 6**.

The results show the high reliability and reproducibility of the method. Also, the suggested first-order derivative spectrophotometric method was compared with the official methods [21-23]. There was no significant difference between the three methods concerning mean values and standard deviations at the 95% confidence level.

TABLE 6: DETERMINATION OF FLURBIPROFEN IN PHARMACEUTICAL PREPARATIONS

Method	Commercial Preparation (100 mg)	λ (nm)	n	Found (mg) X±SD	Recovery (%)	RSD[a] (%)	Confidence Interval	F- test
$1D_{233\ nm}$	Majeski	$1D_{233\ nm}$	6	101.4±3.235	101.4	3.19	101.2-101.7	4.18[a]
	Frolix	$1D_{233\ nm}$	6	100.9±2.896	100.9	2.87	99.9-101.6	
	Maximus	$1D_{233\ nm}$	6	100.2±3.186	100.2	3.18	98.8-101.4	
	Zero-P	$1D_{233\ nm}$	6	101.2±3.764	101.2	3.72	100.5-102.0	
	Fortine	$1D_{233\ nm}$	6	99.8±2.36	99.8	2.36	98.4-101.7	

SD: Standard deviation of six replicate determinations, RSD: Relative standard derivation, [a]Average of six replicate determinations, Ho hypothesis: no statistically significant difference exists between five pharmaceutical preparations, Ho hypothesis is accepted (P > 0.05), [a]Theoretical values at P=0.05

CONCLUSION: In the present report, a simple, rapid, sensitive, reliable, specific, accurate and precise first-order derivative spectrophotometry method for the determination of flurbiprofen in pharmaceutical preparations was developed and validated. Flurbiprofen can be directly determined

in tablets in the presence of excipients without sample pre-treatment procedures by using the first-order derivative spectrophotometric method. The apparatus and reagents used seem to be accessible even for the simple laboratories. Therefore, the developed method can be recommended for routine and quality control analysis of flurbiprofen.

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CONFLICT OF INTEREST: Nil

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