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## VALIDATION OF NOVEL AND COST EFFECTIVE SPECTROSCOPIC METHODS FOR ESTIMATION OF KETOROLAC

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Ketorolac, validation, molar absorptivity, assay, recovery.

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**ABSTRACT:** Sophisticated analytical methods like HPLC and Mass spectroscopic methods which being employed for analysis, are relatively expensive and hence there is a need for developing simple analytical methods. In the proposed work, such methods have been developed and applied for routine determination of ketorolac in pharmaceutical formulations and bulk dosage forms. These methods were based on the formation of colored species on binding of ferric chloride and Hydrochloric acid for method A and binding of drug and Folin Cioclateau reagent in alkaline conditions for method B, and the colored chromogen obtained in each method was finally treated with the drug ketorolac to produce yellow colored for method A and blue colored chromogen for method B with  $\lambda_{\max}$  at 430 nm and 627 nm respectively. Statistical analysis of these methods exhibited Sandell's Sensitivity of 0.8 and 0.0617 (Method A and B) respectively, and the relative standard deviation (RSD) of these methods were found equal to 0.69 and 1.90 respectively, indicating that these methods are highly reproducible, based on the principle of absorption visible spectrophotometry for the determination of ketorolac in formulations and bulk dosage forms.

**INTRODUCTION:** Ketorolac is, 5-benzoyl-2, 3-dihydro-1H-pyrrolizine-1-carboxylic acid which is used to treat osteoarthritis and control acute pain. It is a peripherally acting analgesic. The biological activity of ketorolac tromethamine is associated with the S-form. Ketorolac tromethamine possesses no sedative or anxiolytic properties. Ketorolac or ketorolac tromethamine is a non-steroidal anti-inflammatory drug (NSAID) in the family of heterocyclic acetic acid derivatives, used as an analgesic. Ketorolac was developed in 1989 by Syntex Corp.

(now Roche Bioscience, which is a wholly owned subsidiary of Roche holding Ltd., the parent company of Roche). It was approved by FDA on 30 November 1989 and introduced as Toradol by Syntex. The ophthalmic (i.e., eye-drop) form was approved by FDA on 9 November 1992 and was introduced as Acular eye drops by Allergan under license from Syntex. An intranasal formulation of ketorolac tromethamine was approved by FDA on 14 May 2010 and introduced as Sprix Nasal Spray by Daiichi Sankyo for short-term management of moderate to moderately severe pain requiring analgesia at the opioid level.

In India it is available as Ketanov by Ranbaxy, which is owned by Daiichi Sankyo. Ketorolac acts by inhibiting the bodily synthesis of prostaglandins. Ketorolac in its oral (tablet or capsule) and intramuscular (injected) preparations is a racemic

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mixture of both (S)-(-)-ketorolac, the active isomer, and (R)-(+)-ketorolac. An ophthalmic solution of ketorolac is available and is used to treat eye pain and to relieve the itchiness and burning of seasonal allergies. The structure and chemical name of the drug has been shown in Table 2.01. A very few physico-chemical methods appeared in the literature for the determination of LCD in bulk and pharmaceutical formulations. The literature suggested and reported only a few Spectrophotometric<sup>1-8</sup> techniques, HPLC<sup>9-10</sup>, LC<sup>11,12</sup> for estimation of ketorolac.

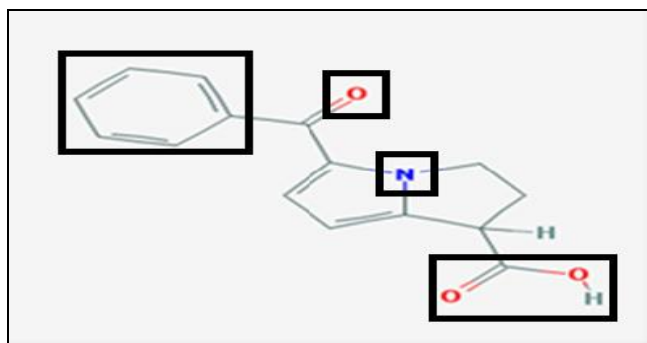


FIG.1: STRUCTURE SHOWING REACTIVE FUNCTIONAL GROUPS

## MATERIALS AND METHODS:

### Instrumentation:

After due calibration of the instrument, spectral and absorbance measurements were made using Thermo UV visible double beam spectrophotometer bearing model number UVA-144294, (Helios alpha) Made in England.

### Preparation of reagents:

All the chemicals used were of analytical grade. All solutions were freshly prepared with distilled water or analytical solvents as the case may be and used for analysis.

**Method A:** Aqueous solutions of various reagents such as ferric chloride (0.7 % w/v), (100 ml diluted with water) were prepared and used.

**Method B:** Aqueous solutions of various reagents such as sodium carbonate (20% w/v) and F/C reagent (1:2 dilution) were prepared and used.

### Standard solution of Ketorolac:

The stock solution (10 ml) of ketorolac was prepared by dissolving 250 mg of the drug in 50 ml of water and made up to 100 ml with water to get a

clear solution. A portion of this stock solution was diluted step wise to get the working standard solutions of varying dilutions ( $M_1$ ,  $M_2$ ).

### Assay procedures:

#### Method A:

Aliquots of standard ketorolac solution (100 $\mu$ g /ml) were transferred into a series of test tubes. The solutions were then made up to the mark with distilled water. After that, 1 ml of enzyme was added and kept aside for 10 min. Then, 2ml of ferric chloride solution was added to each tube and kept aside for 2 min. Next, 1ml of HCl was added to each tube and kept aside for 10 min. Finally the absorbance yellow colored solution was measured against reagent blank at a wavelength of 430 nm.

#### Method B:

Aliquots of standard ketorolac solution (100 $\mu$ g /ml) were transferred into a series of test tube. The solution was then made up to the mark with distilled water. After that, 1ml of enzyme was added and kept aside for 10 min. Then, 2ml of  $\text{Na}_2\text{CO}_3$  was added to each tube and kept aside for 5 min. Next, 1.5ml of FC reagent added to each tube and kept aside for 10 min. Finally the absorbance blue colored solution was measured against reagent blank at a wavelength of 627 nm.

### Recovery with tablet dosage forms:

The contents of tablet dosage forms of toradol, for ketorolac (10 mg), 10 tablets amounting to 100 mg of the formulation were weighed and then transferred to a 100mL volumetric flask. The solution was shaken thoroughly for about 15–20 min. The solution was filtered in Whatman No 1 filter paper, washed well, and the filtrate was transferred into a 100mL volumetric flask and completed to the mark. An aliquot of the solution containing varying dilutions of the formulations were transferred into a 10mL calibrated flask and analyzed applying methods A and B.

**RESULTS AND DISCUSSION:** The results obtained in this method were based on oxidation followed by complex formation. The drug was initially treated with ferric chloride to convert the ferric ions into ferrous ions and then treated under acidic conditions to form a stable yellow color complex for method A and blue colored complex

formation between drug and Folin Cioclateau reagent in alkaline conditions for method B, which exhibited maximum absorption at a wavelength of 430 nm and 627 nm for methods A and B respectively. The absorption spectra of the proposed methods were drawn and are represented in **Fig. 2** and **3** for methods A and B respectively. The Beer's law plots to show linearity for proposed

methods A and B were drawn and are shown in **Fig. 4** and **5** respectively. The optical characteristics such as sandell's sensitivity, molar absorptivity, relative standard deviation and related statistical parameters are shown in **Table 1** and the assay and recovery procedures using the proposed methods for the formulations are shown in **Table 2**.

**TABLE 1: OPTICAL AND REGRESSION CHARACTERISTICS, PRECISION AND ACCURACY OF THE PROPOSED METHODS FOR KETOROLAC**

Parameter	M <sub>1</sub>	M <sub>2</sub>
$\lambda_{\max}$ (nm)	430 nm	627 nm
Beer's law limits (go / ml)	2-10	2-10
Molar absorptivity (L. mole <sup>-1</sup> cm <sup>-1</sup> )	0.0319	0.4135
Sandell's sensitivity (go /cm <sup>2</sup> /0.001 absorbance unit)	0.8	0.0617
Slope (b)	1.08 x 10 <sup>-3</sup>	2.074x 10 <sup>-3</sup>
Intercept (a)	-9.4 x10 <sup>-3</sup>	-0.0323
Correlation coefficient (r)	9999.31	9998.0934
Standard deviation	0.008166	0.005941
% Relative standard deviation	0.69	1.9066
0.05 level	± 0.5769	± 1.5886
0.01 level	± 0.8535	±2.3504

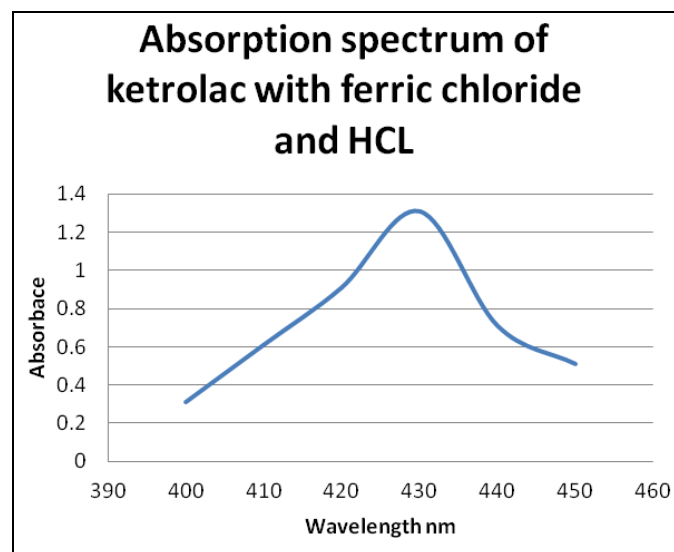
**TABLE 2: ASSAY AND RECOVERY OF KETOROLAC IN DOSAGE FORMS**

Method	Pharmaceutical Formulation	Labeled Amount (mg)	Proposed Method			Found by reference method±SD	% Recovery by proposed methods** ±SD
			Amount found* (mg) ±SD	t	F		
M <sub>1</sub>	Toradol	10	10.005 ± 0.021	0.11	2.31	9.998 ± 0.052	99.93 ± 0.44
M <sub>2</sub>	ketorolac	10	10.012 ± 0.023	0.42	1.87	10.005 ± 0.051	99.67 ± 0.87

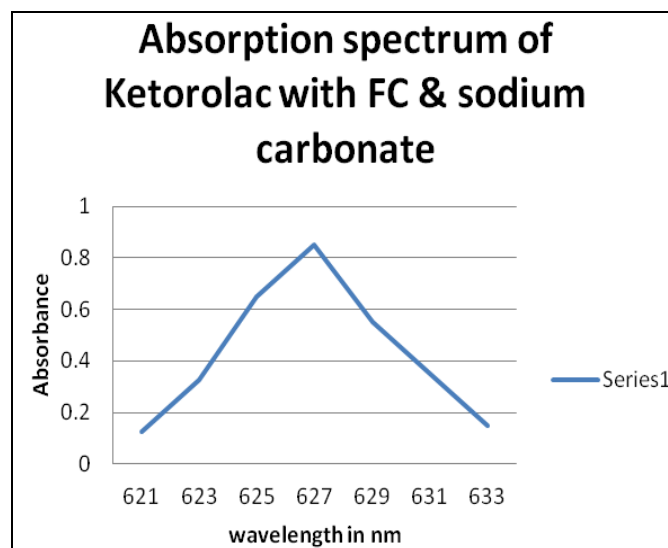
\*Average ± standard deviation of eight determinants the t and F- values refer to comparison of the proposed method.

Theoretical values at 95 % confidence limits t = 2.365 and F = 4.88.

\*\* Average of five determinations



**FIG 2: ABSORPTION SPECTRUM OF KETOROLAC WITH FERRIC CHLORIDE AND HCL**



**FIG. 3: ABSORPTION SPECTRUM OF KETOROLAC WITH FC AND SODIUM CARBONATE**

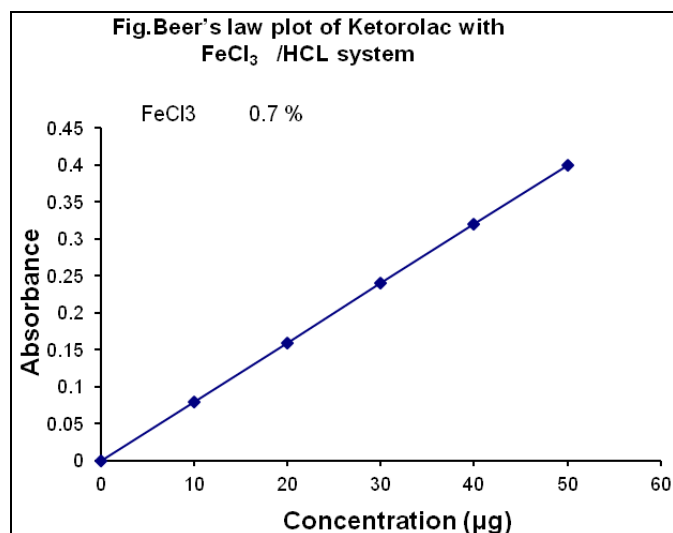


FIG.4: BEER'S LAW PLOT FOR KETOROLAC WITH FERRIC CHLORIDE AND HCL

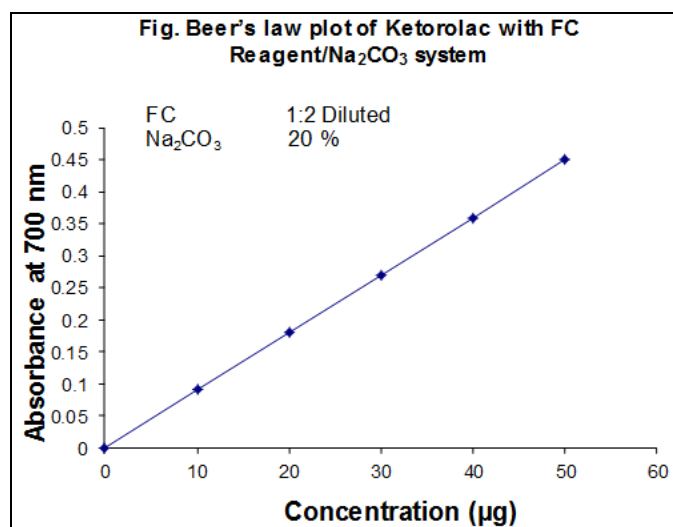


FIG. 5: BEER'S LAW PLOT FOR KETOROLAC WITH FC AND Na<sub>2</sub>CO<sub>3</sub>

**CONCLUSION:** The visible spectrophotometric methods for the determinations of ketorolac in either bulk or pharmaceutical formulations are very valuable. The visible spectrophotometric methods are based on the characteristic properties of different functional groups such as the keto group, amines and the aromatic benzene ring. Each method used a specific reagent and the  $\lambda_{\max}$  and  $\epsilon_{\max}$  values of each method are different. Statistical analysis of the results shows that the proposed methods and procedures have good precision and accuracy. Results of the analysis of the pharmaceutical formulations selected that the proposed methods are suitable for their analysis with virtually no interferences of the usual additives. All the proposed methods (UV-visible

spectrophotometry) are simple, sensitive and reliable and can be used for the routine determination of ketorolac in bulk samples and pharmaceutical formulations depending upon the need of the specific and arising situation.

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