

## Development and Validation of New Analytical Methods for the Determination of Ketorolac Tromethamine (A Non-Steroidal Anti-Inflammatory Agent)

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### Abstract

Five new spectrophotometric methods have been established for the determination of Ketorolac tromethamine in pharmaceutical formulations. Ketorolac tromethamine is Non-steroidal anti-inflammatory drug used to treat pain. Ketorolac tromethamine is chemically known as *k* benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid. Ketorolac has shown absorption maxima at 323 nm in all the methods. Reagents used such as phosphate buffers (pH 5.0 and 8.0), acetate buffer (pH 4.7), 0.1N NaOH and borate buffer (pH 9.0). Ketorolac tromethamine obeys Beer-Lambert's law over the concentration range 5 - 30 µg/ml for all the above mentioned methods and all the methods were validated as per ICH guidelines.

**Keywords:** Ketorolac Tromethamine; Spectroscopy; Phosphate Buffer; Borate Buffer; Acetate Buffer; Sodium Hydroxide, Validation

### Introduction

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug which exhibits pronounced analgesic and moderate anti-inflammatory activity [1]. It is a synthetic pyrrolizine carboxylic acid derivative. Ketorolac tromethamine (Figure 1) is used to treat moderately severe pain and inflammation, usually after surgery [2]. Ketorolac tromethamine works by blocking the production of prostaglandins, compounds that cause pain, fever and inflammation [3]. Ketorolac tromethamine (C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub>) has a molecular weight 376.4 g/mol and it was estimated by various analytical methods such as spectrophotometry [4-6], HPTLC [7,8], voltammetry [9], fluorophotometry [10], HPLC [11-13] and in biological fluids such as human plasma [14], human serum [15], human eye samples [16], serum and synovial fluids [17] and post mortem blood samples [18] in the literature. In the present study the authors have proposed five UV spectrophotometric methods for the determination of Ketorolac tromethamine in pharmaceutical dosage forms and the methods were validated as per ICH guidelines [19].

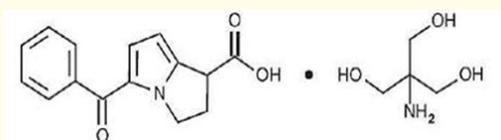


Figure 1: Chemical structure of ketorolac tromethamine.

### Materials and Methods

Double beam spectrophotometer (SHIMADZU Model No. UV - 1800) with quartz cells was used for the present study. All the solutions were scanned at 200 - 400 nm range. Ketorolac tromethamine is available as tablets (Label claim: 10 mg) with brand name KETOROL-DT (Dr. Reddys), DENTAFORCE-DT (Mankind Pharma)

and TORODENT-DT (Cipla Ltd). Ketorolac tromethamine was obtained as a gift sample from Cipla Ltd, India. Reagents such as phosphate buffer (pH 5.0) and phosphate buffer (pH 8.0), acetate buffer (pH 4.7), 0.1N NaOH and borate buffer (pH 9.0) and were prepared as per IP 2010.

### Procedure

25 mg of Ketorolac tromethamine was accurately weighed and transferred in to a 25 ml volumetric flask and dissolved in methanol (1000 µg/ml) and a series of dilutions were prepared with respective buffers as per the requirement. The reagents were prepared as given below.

#### Preparation of phosphate buffer (pH 5.0)

6.8 grams of potassium dihydrogen phosphate was dissolved in water and the pH was adjusted to 5.0 with 10M potassium hydroxide in a 1000 ml volumetric flask.

#### Preparation of phosphate buffer (pH 8.0)

50 ml of 0.2M potassium dihydrogen phosphate was placed in a 200 ml volumetric flask and 46.1 ml of 0.2M sodium hydroxide was added and the volume was made up to 200 ml.

#### Preparation of acetate buffer (pH 4.7)

8.4 grams of sodium acetate and 3.35 ml of acetic acid was dissolved in sufficient water to make 1000 ml in a 1000 ml volumetric flask.

#### Preparation of 0.1N sodium hydroxide

4 grams of sodium hydroxide was dissolved in sufficient water and made up to 1000 ml in 1000 ml volumetric flask.

#### Preparation of borate buffer (pH 9.0)

6.20 grams of boric acid was dissolved in 500 ml of water and the pH was adjusted with 1M sodium hydroxide (about 41.5 ml)

and diluted with water to produce 1000 ml in a 1000 ml volumetric flask.

**Method validation**

**Linearity**

A series of Ketorolac tromethamine solutions 5 - 30 µg/ml were prepared using different buffer solutions - phosphate buffer pH 5 (Method I), phosphate buffer pH 8 (Method II), acetate buffer pH 4.7 (Method III), 0.1 N sodium hydroxide (Method IV) and borate buffer pH 9 (Method V) and scanned against their reagent blank at range of 200 - 400 nm. Ketorolac tromethamine has shown its λ<sub>max</sub> at 323 nm in all methods. A calibration curve was drawn by taking the concentration on the X-axis and their respective absorbance on the Y-axis for all the methods.

**Precision and accuracy**

Precision was studied by measuring the absorbance of 6 solutions of the same concentration (n = 6) and there by mean, standard deviation and relative standard deviation were calculated. Accuracy was studied by spiking the formulation solution of a fixed concentration with pure drug solution (50%, 100% and 150%) by standard addition method and there by percentage recovery and relative standard deviation were calculated.

**Assay of ketorolac tromethamine tablets**

20 tablets of Ketorolac tromethamine of two different brands were procured from the local pharmacy store and extracted with methanol and further dilutions were made with respective buffers and assay was carried out for all the methods.

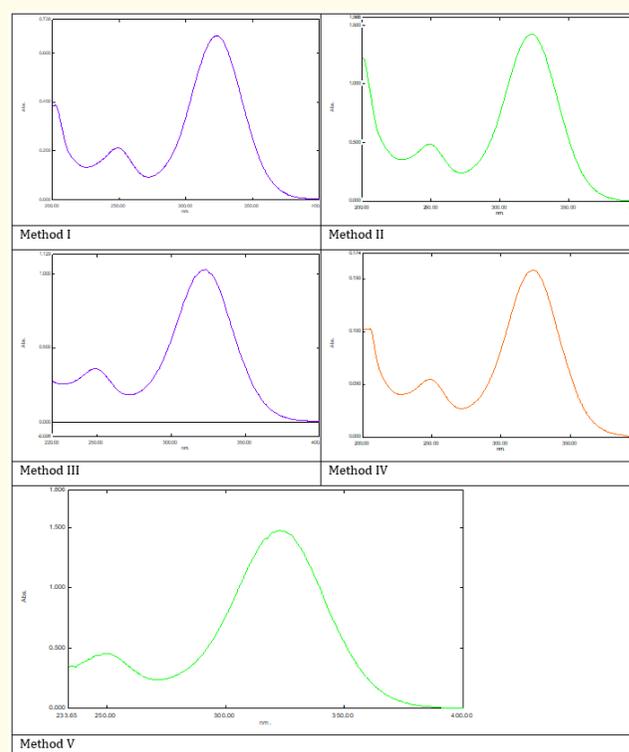
**Results and Discussion**

New spectrophotometric methods were developed for the determination of Ketorolac tromethamine in different reagents such as phosphate buffer (pH 5.0) (Method I), phosphate buffer (pH 8.0) (Method II), acetate buffer (pH 4.7) (Method III), NaOH (Method IV) and borate buffer (pH 9.0) (Method V) respectively. The present methods were compared with the previously published spectrophotometric methods and summarized in table 1.

Reagent	λ <sub>max</sub> (nm)	Linearity (µg/mL)	Ref
Distilled water	322	2 - 14	4
Ninhydrin	570	50 - 250	5
2,4-dinitrophenyl hydrazine (Condensation reaction)	424	0.5 - 18.5	6
7,7',8,8' Tetra cyano quinodimethane (Charge transfer reaction)	842	2.0 - 50.0	
Phosphate buffer (pH 5.0)	323	5 - 30	Present methods
Phosphate buffer (pH 8.0)			
Acetate buffer (pH 4.7)			
0.1N NaOH			
Borate buffer (pH 9.0)			

**Table 1:** Review of spectrophotometric methods.

The absorption spectrum of Ketorolac tromethamine has shown λ<sub>max</sub> at 323 nm in all the reagents (Figure 2). Ketorolac tromethamine obeys Beer-Lambert's law over the concentration range 5 - 30 µg/ml in all the methods (Table 2). Calibration curves were drawn by taking the concentration on the x-axis and the corresponding absorbance on the y-axis. The linear regression equations are found to be y = 0.0735x - 0.0214 (0.9978), y = 0.067x - 0.0023 (0.9983), y = 0.066x + 0.0158 (0.9992), y = 0.0733x - 0.0007 (0.9994), y = 0.0764x - 0.0024 (0.9966) in phosphate buffer (pH 5.0), phosphate buffer (pH 8.0), acetate buffer (pH 4.7), 0.1N NaOH and borate buffer (pH 9.0) respectively (Figure 3). The percentage RSD in precision and accuracy was found to be < 2 in all the above methods indicating that the methods are accurate and precise. The Optical characteristics of Ketorolac tromethamine were shown in table 3. The percentage of purity (Assay) results of Ketorolac tromethamine in the marketed formulations were shown in table 4 and no interference of excipients was observed.



**Figure 2:** Absorption spectra of ketorolac tromethamine (20 µg/ml).

Conc. (µg/ml)	Absorbance				
	Method I	Method II	Method III	Method IV	Method V
5	0.331	0.346	0.343	0.374	0.357
10	0.671	0.717	0.677	0.741	0.745
15	1.005	1.064	1.02	1.217	1.097
20	1.352	1.429	1.374	1.501	1.482
25	1.612	1.762	1.65	1.837	1.793
30	2.044	2.246	1.976	2.338	2.218

**Table 2:** Linearity of Ketorolac tromethamine.

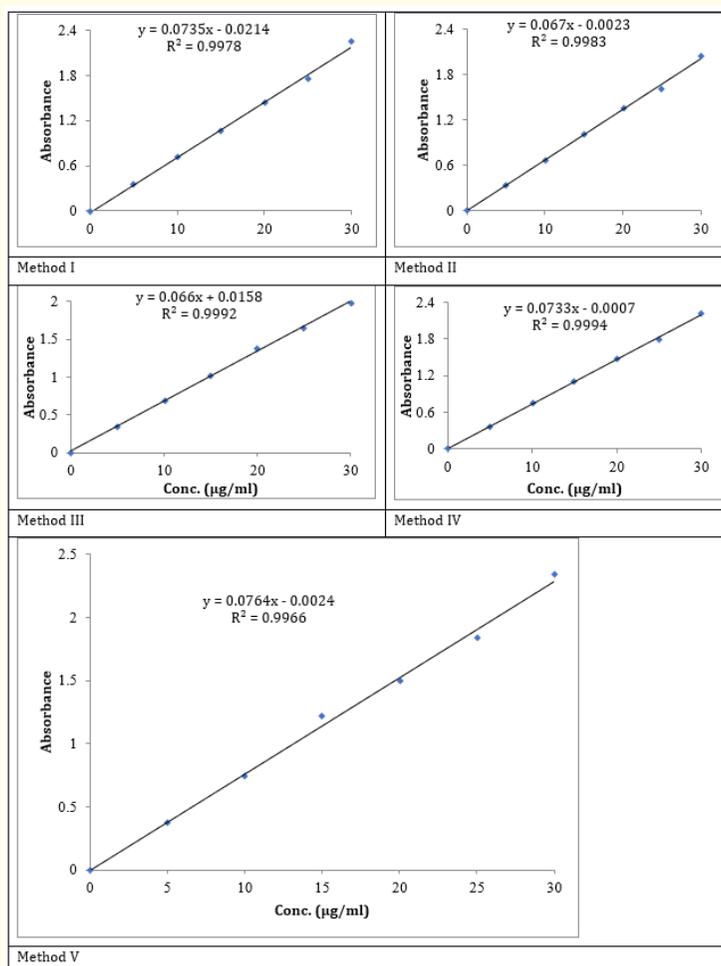


Figure 3: Calibration curves of ketorolac tromethamine.

Parameters		Method I	Method II	Method III	Method IV	Method V
Linearity (µg/ml)		5 - 30	5 - 30	5 - 30	5 - 30	5 - 30
$\lambda_{max}$ (nm)		323	323	323	323	323
Molar extinction coefficient (litre/ mole/ cm <sup>-1</sup> )		$2.525 \times 10^4$	$2.6987 \times 10^4$	$2.5482 \times 10^4$	$2.7891 \times 10^4$	$2.8041 \times 10^4$
Sandell's sensitivity (µg/cm <sup>2</sup> /0.001 absorbance unit)		0.01490	0.01394	0.01477	0.01349	0.01342
Slope		0.0735	0.067	0.066	0.0733	0.0764
Intercept		- 0.0214	- 0.0023	0.0158	- 0.0007	- 0.0024
Correlation coefficient		0.9978	0.9983	0.9992	0.9994	0.9966
Precision (%RSD)	Intraday	0.81 - 1.02	0.82 - 1.24	0.77 - 0.91	0.83 - 1.18	0.87 - 1.24
	Interday	0.83 - 0.92	0.78 - 1.21	0.71 - 0.93	0.88 - 1.13	0.69 - 1.28
Accuracy (% RSD)		0.91 - 1.22	0.87 - 1.18	0.63 - 0.89	0.58 - 0.99	0.57 - 0.96

Table 3: Optical characteristics of Ketorolac tromethamine.

Brand	Method I		Method II		Method III		Method IV		Method V	
	Observed amount (mg)	% Recovery								
I	99.82	99.85	99.80	99.89	99.92	99.889	99.93	99.91	99.92	99.91
II	99.86	99.83	99.85	99.85	99.91	99.91	99.90	99.788	99.84	99.94

Table 4: Assay of ketorolac tromethamine (Label claim: 10 mg).

\*Mean of three replicates.

## Conclusion

These five new spectrophotometric methods were validated and applied for the estimation of Ketorolac tromethamine in pharmaceutical formulations i.e. Tablets. The proposed methods are simple, precise, accurate, and economical. These methods can be successfully applied for the determination of Ketorolac tromethamine in pharmaceutical dosage forms and also for the kinetic studies of the biological samples.

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