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Original Article

RATIO SPECTRA DERIVATIVE UV SPECTROPHOTOMETRIC METHOD FOR SIMULTANEOUS ESTIMATION OF KETOROLAC TROMETHAMINE AND PHENYLEPHRINE HYDROCHLORIDE IN IMMEDIATE RELEASE TABLET

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ABSTRACT

Objective: To develop and validate robust, accurate and precise UV spectrophotometric method for determination of Ketorolac Tromethamine and Phenylephrine Hydrochloride.

Methods: Ratio spectra derivative method was developed using water as solvent. The developed method was validated as per International Conference on Harmonization (ICH) guidelines.

Results: Linearity of the developed method was 0.9958 and 0.9987 in the range of 4-20 ppm and 12-60 ppm for Ketorolac Tromethamine and Phenylephrine Hydrochloride respectively. % Relative standard deviation (RSD) was found to be less than 2 for Intraday precision and Intermediate precision. % recovery was found to be 98.5–100.27 % and 98.38–101.99 % for Ketorolac Tromethamine and Phenylephrine Hydrochloride respectively.

Conclusion: A robust, accurate and precise UV spectrophotometric method was developed and validated as per ICH guidelines.

Keywords: Ketorolac Tromethamine, Phenylephrine Hydrochloride, UV spectroscopy, Ratio spectra derivative method.

INTRODUCTION

Ketorolac Tromethamine, chemically known as 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid with 2-amino-2-(hydroxymethyl) propane-1,3-diol (fig. 1), is a Non-steroidal anti-inflammatory drug. Ketorolac Tromethamine is used as an analgesic and antipyretic agent. It is freely soluble in water and methanol.

Ketorolac Tromethamine is official in IP, BP and USP and estimated by Potentiometric Titration as per IP [1] and BP [2] and HPLC as per USP [3]. Literature survey showed several reported spectro-photometric [4, 5] and HPLC [6, 7] methods for determination of Ketorolac Tromethamine in pharmaceutical dosage form either as the single component or in combination with other drugs.

Phenylephrine Hydrochloride, chemically known as R)-1-(3-Hydroxy phenyl)-2-methyl amino ethanol hydrochloride (fig. 2), is a sympathomimetic drug. Phenylephrine Hydrochloride is used as an anti-allergic agent. It is freely soluble in water and methanol [8].Phenylephrine Hydrochloride is official in IP, BP and USP and estimated by potentiometric titration as per IP [9] and BP [10] and Titration as per USP [11].

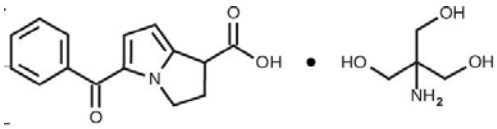

Fig. 1: Structure of ketorolac tromethamine

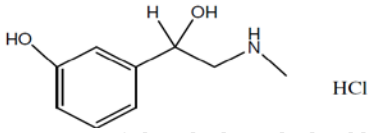

Fig. 2: Structure of phenylephrine hydrochloride

Literature survey showed several reported spectrophotometric [12, 13] and HPLC [14, 15] methods for determination of Phenylephrine Hydrochloride in pharmaceutical dosage form either as the single component or in combination with other drugs [16, 17]. There are no UV methods available for simultaneous estimation of Ketorolac Tromethamine and Phenylephrine Hydrochloride in combination.

So the rational this works to develop robust, accurate and precise UV method for simultaneous estimation of Ketorolac Tromethamine and Phenylephrine Hydrochloride in immediate release tablet.

MATERIALS AND METHODS

Materials

Instrument

UV visible spectrophotometer (Shimadzu, model 1800) with UV probe software was used for recording the spectra and measuring the absorbance.

Chemicals and reagents

Ketorolac Tromethamine was supplied by the Cadila healthcare, Ahmedabad as the gift sample. Phenylephrine Hydrochloride was supplied by the Tuton Pharmaceuticals, Mumbai as the gift sample. For the preparation of solution double distill water was used.

Methods

Selection of solvent

Double distil water was used as a solvent for the preparation of the sample solution.

Selection of method

Standard solution of Ketorolac Tromethamine (4.2 µg/ml) and Phenylephrine Hydrochloride (12.6 µg/ml) was scanned separately in the range of 200-400 nm. From the overlay spectra of Ketorolac Tromethamine and Phenylephrine Hydrochloride, Absorbance correction method, Absorbance ratio and derivative spectroscopic

method are possible. But in all these methods % recovery was found out of the limit. So that Ratio spectra derivative spectroscopic method was developed.

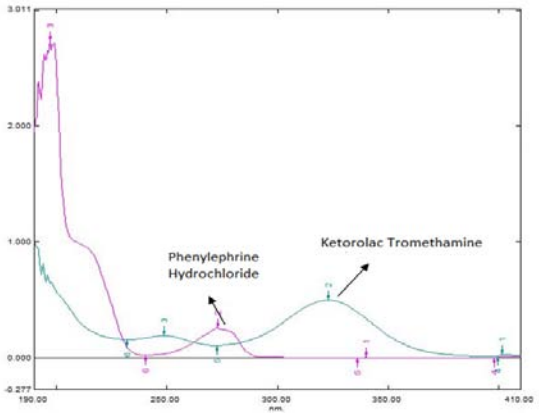

Fig. 3: Overlay spectra of ketorolac tromethamine and phenylephrine hydrochloride

Ratio spectra derivative spectroscopic method

Selection of wavelength

4µg/ml of Ketorolac Tromethamine and 12µg/ml Phenylephrine Hydrochloride were scanned separately in the range of 200-400 nm. For this method development, Ketorolac Tromethamine (12 µg/ml) and Phenylephrine Hydrochloride (36 µg/ml) were used as devisor and first derivative spectra were traced using 1 scaling factor. From the first derivative ratio spectra, 290 nm selected for the Ketorolac Tromethamine (fig. 4) and 227 nm selected for the Phenylephrine Hydrochloride (fig. 5).

Preparation of stock solution for ketorolac tromethamine (100 µg/ml)

A stock solution of 100 µg/ml of Ketorolac Tromethamine was prepared by accurately weighing 10 mg of Ketorolac Tromethamine and transferred in 100 ml volumetric flasks. 50 ml of water was added in the volumetric flask and the drug was dissolved properly and then the volume was made up to 100 ml with water.

Preparation of stock solution for phenylephrine hydrochloride (100 µg/ml)

A stock solution of 100 µg/ml of Phenylephrine Hydrochloride was prepared by accurately weighing 10 mg of Phenylephrine Hydrochloride and transferred in a 100 ml volumetric flask. 50 ml of water was added in the volumetric flask and the drug was dissolved properly and then the volume was made up to 100 ml with water.

Preparation of sample solution

Twenty tablets were weighed; average weight was determined and finely powdered. An accurately weighed quantity of tablet powder equivalent to 4.2 mg Ketorolac Tromethamine and 12.6 mg Phenylephrine Hydrochloride was transferred to 100 ml volumetric flask and 50 ml of water was added and dissolved by sonication for 30 min and then volume up was made up to the mark with water. Then solution is filtered through whatman filter paper. 1 ml of filtrate was taken in a 10 ml of volumetric flask and volume was made up to mark with water. The above mixture was analysed in UV spectrophotometer. % assay was calculated. Results are reported in table 6.

RESULTS AND DISCUSSION

Selection of wavelength

4µg/ml of Ketorolac Tromethamine and 12µg/ml Phenylephrine Hydrochloride were scanned separately in the range of 200-400 nm. For this method development Ketorolac Tromethamine (12 µg/ml) and Phenylephrine Hydrochloride (36 µg/ml) were used as devisor and first derivative spectra were traced using 1 scaling factor. From the first derivative ratio spectra, wavelength selected were 290 nm for Ketorolac Tromethamine and 227 nm for Phenylephrine Hydrochloride.

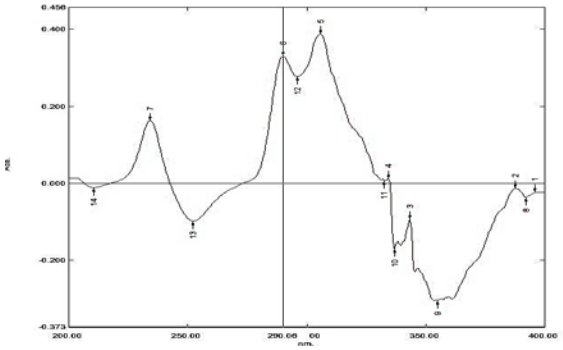

Fig. 4: First derivative ratio spectra of Phenylephrine Hydrochloride (12µg/ml), divisor Ketorolac Tromethamine (12µg/ml)

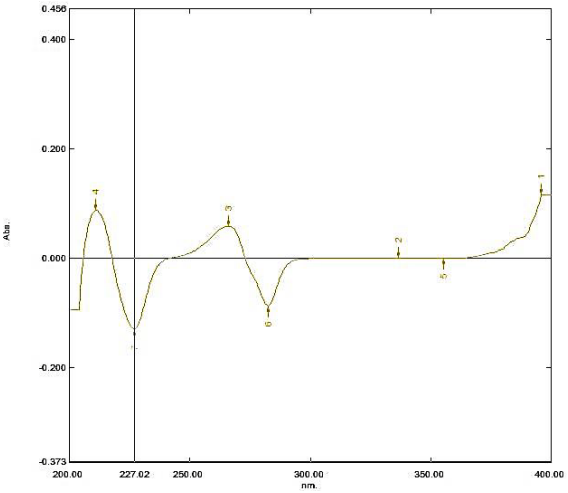

Fig. 5: First derivative ratio spectra of ketorolac tromethamine (4 µg/ml), divisor phenylephrine hydrochloride (36 µg/ml)

Validation of ratio spectra derivative spectroscopic method

Linearity and range

Linearity study was carried out for both the drugs at different concentration levels. Linearity of Ketorolac Tromethamine and Phenylephrine Hydrochloride was in the range of 4-20 µg/ml and 12-60 µg/ml and results are reported in following table.

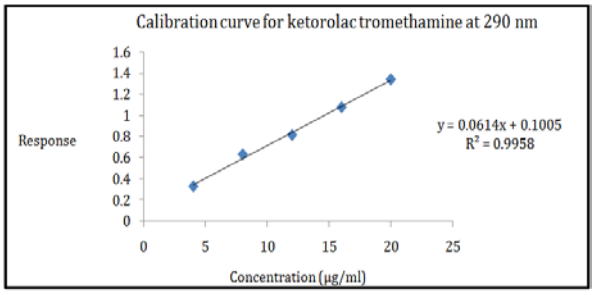

Fig. 6: Calibration curve for ketorolac tromethamine at 290 nm

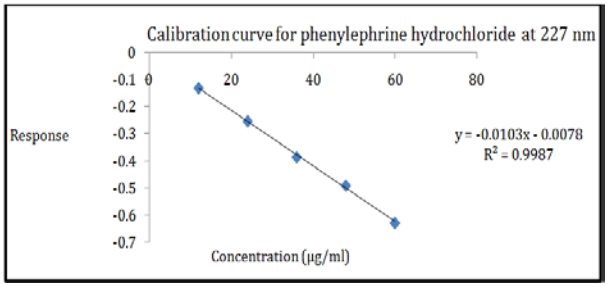

Fig. 7: Calibration curve for phenylephrine hydrochloride at 227 nm

Precision

Intraday precision

Three replicates of three concentration of standard solution of Ketorolac Tromethamine (8, 12 and 16 µg/ml) and Phenylephrine Hydrochloride (24, 36 and 48 µg/ml), total nine determination were analysed at three consecutive times on same day and absorbance was measured. % RSD was found to be within acceptable limit that is<2 %. The data for intraday precision of are reported in table 2.

Intermediate precision

Inter day precision

Three replicates of three concentration of standard solution of Ketorolac Tromethamine (8, 12 and 16 µg/ml) and Phenylephrine Hydrochloride (24, 36 and 48 µg/ml), total nine determination were analysed at three consecutive day and absorbance was measured. % RSD was found to be within acceptable limit that is<2 %. The data for inter day precision of are reported in table 2.

Different instruments

Three concentration of standard solution of Ketorolac Tromethamine (8, 12 and 16 µg/ml) and Phenylephrine Hydrochloride (24, 36 and 48 µg/ml) were analysed by two different instruments (UV-1800 and UV-1700) on a single day and absorbance was measured. % RSD was found to be within acceptable limit that is<2 %. The data are reported in table 2.

Different analysts

Three concentrations of the standard solution of Ketorolac Tromethamine (8, 12 and 16 µg/ml) and Phenylephrine Hydrochloride (24, 36 and 48 µg/ml) were analysed by three different analysts and absorbance was measured. % RSD was found to be within acceptable limit that is<2 %. The data for different analyst are reported in table 2.

Table1: Data for linearity and range

Ketorolac tromethamine		**Phenylephrine hydrochloride**	
Concentration (µg/ml)	**Response at 290 nm (n=5)**	**Concentration (µg/ml)**	**Response at 227 nm (n=5)**
4	0.330	12	-0.131
8	0.632	24	-0.253
12	0.812	36	-0.386
16	1.075	48	-0.491
20	1.337	60	-0.629
Regression equation	y = 0.0614x+0.1005	Regression equation	y =-0.0103x-0.0078
R^2 value	0.9958	R^2value	0.9987

Table 2: Precision data for ketorolac tromethamine and phenylephrine hydrochloride

Precision	**Concentration (µg/ml)**		**% RSD**	
	Ketorolac Tromethamine	**Phenylephrine Hydrochloride**	**Ketorolac Tromethamine**	**Phenylephrine Hydrochloride**
Intraday precision (n=3)	8	24	0.34	0.37
	12	36	0.09	0.52
	16	48	0.11	1.00
Inter day precision (n=3)	8	24	0.78	0.81
	12	36	1.20	0.80
	16	48	0.16	1.28
Different instrument precision (n=2)	8	24	0.55	0.78
	12	36	0.74	0.64
	16	48	0.42	1.00
Different analyst precision (n=3)	8	24	0.94	0.67
	12	36	1.16	1.06
	16	48	0.33	0.58

Table 3: Accuracy data for ketorolac tromethamine and phenylephrine hydrochloride

Level	**% Recovery**	
	Ketorolac tromethamine	**Phenylephrine hydrochloride**
80 % (n=3)	100.17	99.51
100 % (n=3)	98.87	100.37
120 % (n=3)	100.20	100.50

Accuracy

Accuracy study was performed using the placebo. The accuracy of the method was tested by 3 replicate analyses of 3 different levels (80%, 100% and 120%). Accuracy was determined by % recovery study. % recovery was found to be 98.19–100.71 % and 98.50–101.72% for Ketorolac Tromethamine and Phenylephrine Hydrochloride respectively. The data of accuracy are reported in following table.

Limit of detection (LOD) and limit of quantitation (LOQ)

LOD and LOQ were determined by repeating the calibration curve five times. The results of LOD and LOQ are reported in following table.

Table 4: Data of LOD and LOQ

Parameter	Ketorolac tromethamine	Phenylephrine hydrochloride
S. D. of five intercept	0.01703	0.00133
Mean of five slope	0.215	0.0102
LOD(µg/ml)	0.261	0.433
LOQ(µg/ml)	0.792	1.30

Table 5: Robustness data for ketorolac tromethamine and phenylephrine hydrochloride

Drug	Concentration (µg/ml)	% RSD
Ketorolac tromethamine	8	0.91
	12	1.57
	16	1.36
Phenylephrine hydrochloride	24	1.16
	36	1.27
	48	1.24

Table 6: Data for analysis of IR tablet by UV method

Tablet	Dose	Amount found (mg) (mean±SD) (n=3)	% amount found (mean±SD) (n=3)
Ketorolac tromethamine	4.2 mg	4.21±0.02	100.36±0.59
Phenylephrine hydrochloride	12.6 mg	12.73±0.19	99.53 ±1.51

Robustness

Three concentrations of the standard solution of Ketorolac Tromethamine (8, 12 and 16 µg/ml) and Phenylephrine Hydrochloride (24, 36 and 48 µg/ml) were analysed at 3 different wave length and % RSD was calculated. % RSD was found to be within acceptable limit that is <2 %. The data for Robustness (different wavelength) are reported in the following table.

Analysis of drugs in immediate release tablet

Analysis of drugs in immediate release (IR) tablet was done by UV method and the % Assay was calculated. % amount of both the drug was found within the limit that is 98-102%.

CONCLUSION

In present work, ratio spectra derivative spectroscopic method was developed for simultaneous estimation of Ketorolac Tromethamine and Phenylephrine Hydrochloride in using water as a solvent. The developed method is robust, accurate and precise. The method is successfully validated as per ICH guidelines.

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CONFLICT OF INTERESTS

Declared None

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