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DEVELOPMENT AND VALIDATION OF UV-VISIBLE SPECTROPHOTOMETRIC METHOD FOR ESTIMATION OF KETOPROFEN IN CAPSULE AND TABLET DOSAGE FORMS

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ABSTRACT

A simple and sensitive UV-spectrophotometric method for the assay of the poorly water-soluble ketoprofen in its dosage form was developed using 1M $NaHCO_3$ as diluent. Ketoprofen exhibited maximum absorbance at 260 nm. Validation of the method was performed according to ICH guidelines. It was found to be linear in the concentration range of 2.5-15 µg/ml (R^2=0.998) with low values of limit of detection and quantification (0.78µg/ml, 2.35µg/ml).The application of the proposed method for assay of ketoprofen (tablets and capsules) gave good results 99.08%±0.58 and 99.28%± 0.82, respectively.

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INTRODUCTION

Ketoprofen (Figure1) is a derivative of propionic acid with non-steroidal anti-inflammatory activity (NSAID).The antipyretic effect is due to a resetting of hypothalamic thermoregulatory center, whereas the anti-inflammatory and analgesic effects are due to inhibition of prostaglandin synthesis [1]. Like most NSAIDs, ketoprofen is advantageous because it lacks addictive potential and does not result in sedation or respiratory depression [2].

Ketoprofen has pKa of 5.94 for the COOH functional group. It is practically insoluble in water but soluble in aqueous solution of alkali hydroxides and carbonates and freely soluble in alcohol, acetone and dichlormethane [3].

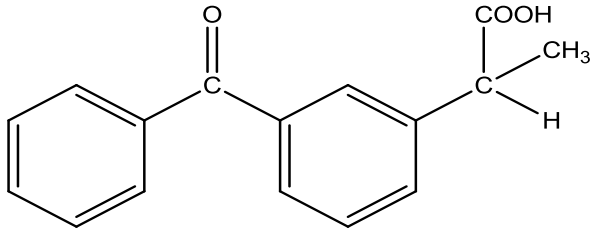


Figure 1: Chemical structure of Ketoprofen.

Increasing the aqueous solubility of insoluble and slightly soluble drugs has been done by various methods to avoid the use of the costly and toxic organic solvents. The development of alternative means for solubilizing these drugs, so as to develop simple methods for their assay is highly preferred particularly in developing countries.

Maheshwari *et al*. have proposed the application of hydrotropy agents in titrimetric and spectrophotometric estimation of a large number of poorly water-soluble drugs, discouraging the use of organic solvents [4-10]. Sodium benzoate, sodium salicylate, sodium ascorbate, niacinamide, sodium citrate and urea are the most popular examples of hydrotropic agents that have been used to solubilize poorly water-soluble compounds. Several methods have been described for ketoprofen determination in pharmaceutical formulations and serum including UV spectrophotometry [11], reverse phase liquid chromatographic (RP-LC) [12], capillary electrophoresis [13] and fourier transform infrared spectrometry (FT-IR) [14].

Therefore, the aim of the present work was to develop a simple, sensitive, precise and accurate spectrophotometric method that could be applied in quality control for the routine analysis of poorly soluble ketoprofen in tablets /capsules using simple solvent (1M $NaHCO_3$).

MATERIALS AND METHODS

Chemicals and Reagents

All chemicals and solvents used were of analytical grade. Ketoprofen was obtained as a gift sample from local factory. Ketoprofen tablets/capsules were purchased from the local market.

Instrument

A UV-min-1240 spectrophotometer (Shimadzu, Kyoto, Japan) with 1 cm matched silica cells was used for the spectrophotometric analysis.

Preparation of diluent solvent (sodium hydrogen carbonate (1M))

84.01g of sodium hydrogen carbonate was dissolved in about 700ml distilled water. The resultant solution was transferred into 1L volumetric flask and thoroughly shaken until completely dissolved. The volume was then completed to mark with distilled water.

Construction of calibration curve

Series of ketoprofen concentrations in the range 2.5 - 15µg/ml was prepared. Calibration curve was constructed by plotting the measured absorbance values at 260nm against the respective concentration. Regression analysis data was calculated according to the following equation [15]:

$$y = (b \pm ts_b)\, x + (a \pm ts_a)$$

Where b is the slope, a is the intercept, s_b is the standard deviation of the slope, s_a is the standard deviation of intercept, t is the t-value at 95% confidence level for (n–2) degrees of freedom.

Furthermore, limits of detection and quantification were calculated from the obtained regression data using the following formulae [16]:

$$LOD = 3.3\,\sigma/S \qquad \text{and} \qquad LOQ = 10\,\sigma/S$$

Where σ = the standard deviation of the response, S = the slope of the calibration curve

PRECISION

The precision of the method was evaluated by both interday and intraday variation studies (three concentration/ three replications) as well as the relative standard deviation (%RSD).

Accuracy:

Standard addition and percent recovery methods was used to evaluate the accuracy of the developed method. Sample was spiked at three levels of standard of quantity equivalent to 50, 100 and 150%. The recovery % was then determined using the following formula [17]:

$$\%\ recovery = (Cs - Cu)/CA \times 100$$

Where Cs =concentration of spiked samples, Cu = concentration of unspiked samples, CA = concentration of analyte added to the test sample

Assay of Ketoprofen brands

Ten ketoprofen tablets (labeled 100mg / table) were weighed and ground. An amount equivalent to 10mg of ketoprofen was accurately weighed and dissolved in diluents solvent. Solution was shaken thoroughly for 10 minutes and transferred into 100ml volumetric flask. Finally the volume was completed to mark and filtered. Further dilution was carried from the obtained solution to produce a concentration of 10µg/ml. The absorbance values of five replicates were measured at 260nm against blank. The % content of each brand was determined using calibration curve or direct sample/ standard comparison. Procedure was repeated for ketoprofen capsules (labeled 50mg / capsule).

RESULTS

Method validation:

The proposed method was validated, as per ICH guidelines, with respect to linearity, limit of detection and limit of quantification, precision and accuracy.

Linearity

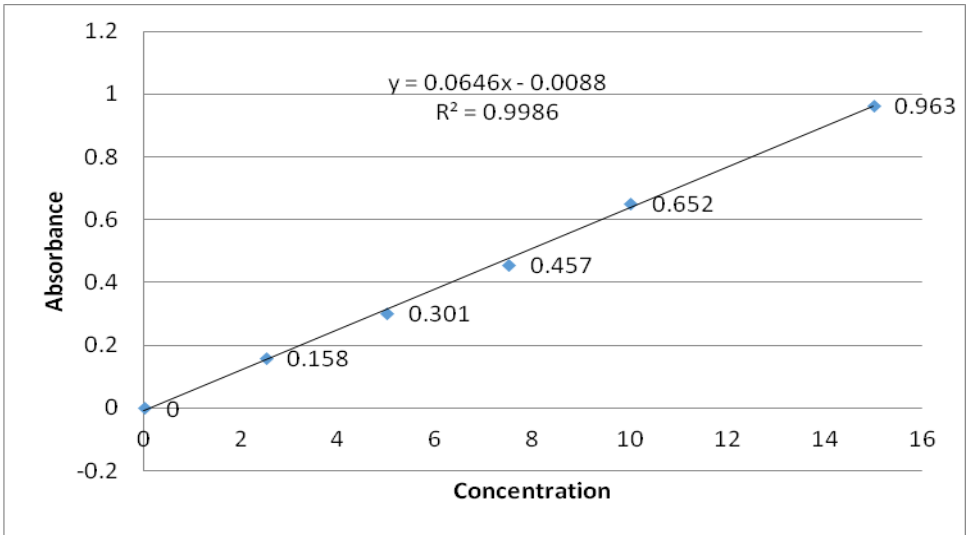


Figure 2: Calibration curve of Ketoprofen standard.

Table 1: Regression analysis data of the developed method.

Parameter	Developed method
λ_{max} (nm)	260nm
Concentration range (µg/ml)	2.5-15µg/ml
Slope± SE*	0.064±0.00167
Intercept± SE *	-0.008±0.0013
Limit of detection (µg/ml)	0.78
Limit of quantification (µg/ml)	2.35
A1% 1cm	646
Correlation coefficient (r2)	0.998

*Standard error of slope and intercept calculated at 95% confidence limit for n-2 degrees of freedom

Precision

Table 2: Represents the intraday and interday precision data (n=3).

Precision	Mean%	Standard deviation	%RSD
Intraday	98.60	0.69	0.70
Interday	97.76	0.73	0.75

Accuracy

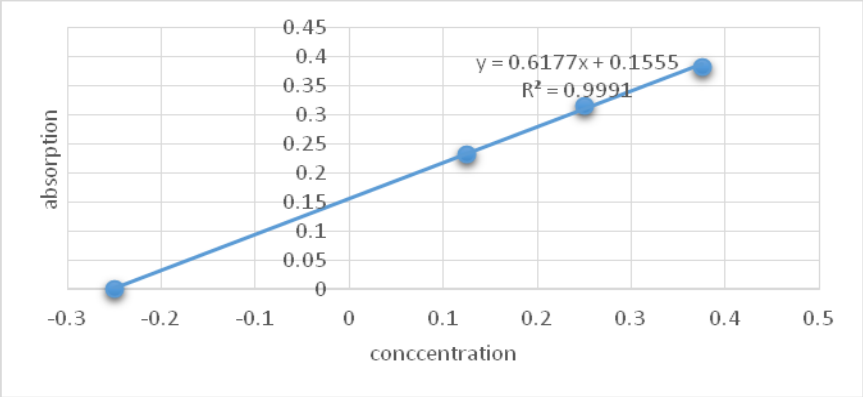


Figure 3: Standard addition method plot.

Table 3: Represents the recovery percent data (n=3).

	Absorbance values			Found concentration	% Recovery ± RSD%
50% Level	0.227	0.236	0.233	0.252	101.05% ± 0.53
100% Level	0.301	0.311	0.326	0.253	101.32%± 0.08
150% Level	0.382	0.390	0.374	0.248	99.26%± 0.04

Assay of ketoprofen of marketed formulations

Table 4: Assay data of ketoprofen formulations with statistical evaluation (n=5).

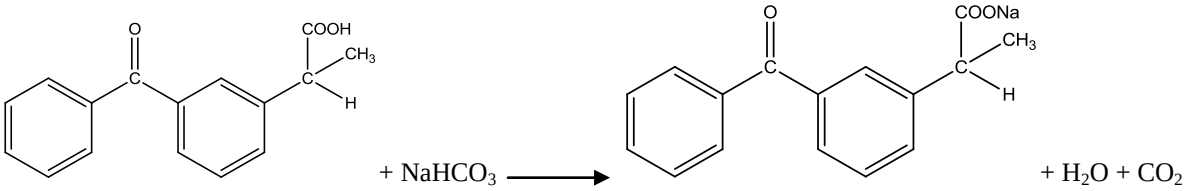
Formulation	Labeled claim(mg)	Measured of claim as mean %± SD
Tablets	100	99.08%±0.58
Capsules	50	99.28%± 0.82

DISCUSSION

Development of analytical method is crucial to counteract for limitation of official methods in terms of cost, sensitivity and accuracy in order to assure delivery of drugs with adequate quality and safety to the patient.

This study is an attempt to develop a simple, accurate, precise and cost effective spectrophotometric method for estimation of ketoprofen tables /capsules dosage forms using simple solvent system and available UV-visible spectrophotometer.

Ketoprofen has a carboxylic functional group in its chemical structure making it soluble in aqueous solution of alkali hydroxides and carbonates. Ketoprofen is soluble in $NaHCO_3$ in a reaction producing carbon dioxide and sodium salt of the drug, which is soluble in water (Scheme 1). Therefore, this reaction has advantage of solubilizing the drug as well as identification test of the drug depending on the carboxylic functional group. In addition, Ketoprofen with its extended chromophore system is considered a good candidate for assay using UV-spectrophotometry with high sensitivity.



Scheme 1: Solubilization of Ketoprofen.

Sodium hydroxide and sodium carbonate are strong bases that have high solubilizing property for acid like ketoprofen; however using these salts as solvent for tablets materials can lead to dissolving unwanted materials with tablets/capsules matrixes which can lead to interference in the assay. That is why sodium hydrogen carbonate was chosen as solubilizing agent in this work as it is a weak base that has less solubilizing properties than these two strong bases.

It worth noting that the useful method developed by Veena and Mithun, 2010 (11) for the assay of ketoprofen used three mixed hydrotropy reagents for solubilizing the drug before the assay. This system has advantages over the other reported methods as it utilizes a nontoxic solvent and does not involve tedious sample preparation or necessitates the provision of a critical reaction conditions.

Linearity

The constructed calibration curve was found to be linear in the range 2.5-15µg/ml with correlation coefficient 0.998 and linear regression equation *y=0.6535x-0.0166*. This indicated an excellent correlation existed between the absorbance and concentration of ketoprofen.

The obtained values of LOD and LOQ were 0.778 and 2.35µg/ml, respectively. Thus indicating that this is the minimum detectable and quantification amount of ketoprofen can be determined with a suitable precision and accuracy (Table 1).

Precision

The precision of the method was evaluated by both interday and intraday variation studies (three concentration/ three replications) as well as the relative standard deviation (%RSD). The RSD% values were <2.0% reflecting that the developed method is precise (Table 2).

Accuracy

The accuracy was assessed in terms of standard addition method (Figure 3) and recovery percentage at three levels (Table 3). The obtained results were within over all range between (99-101%). These indicate high accuracy of the developed method and freedom of interference from the formulation matrix

Assay of ketoprofen of marketed formulations:

Table 5 reflects the results of the assay of ketoprofen tablets and capsules (99.08%±0.58 and 99.28%± 0.82, respectively) which indicate good assay results of the formulations.

CONCLUSION

The developed method as validated by the ICH guidelines was proved to be sensitive, accurate and precise. Application to actual drugs formulations gave results with acceptable RSD value (<2%). The simplicity and safety of the developed method encourage its application in QC labs for the routine analysis of ketoprofen formulations.

CONFLICT OF INTEREST

Authors declare no conflict of interest

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