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DEVELOPMENT AND VALIDATION OF UV SPECTROSCOPIC AND RP-HPLC METHODS FOR ESTIMATION OF DEXKETOPROFEN TROMETAMOL IN TABLET DOSAGE FORM

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ABSTRACT

The study is focused to developed and validate a UV-Spectroscopic method and HPLC Method for simultaneous estimation of Dexketoprofen Trometamol from their dosage form. Equation is applied in spectroscopic method, in which wavelengths, 260nm has been been selected. At this wavelength drug have considerable absorbance. The method was found to be linear in range of 2-12µg/mL for Dexketoprofen Trometamol. The accuracy and precision were determined and validated statistically.

A simple Reverse Phase Liquid Chromatographic method has been developed and validated for determination of Dexketoprofen Trometamol. The separation was carried out using mobile phase consisting of Phosphate buffer: Methanol (30:70). The column was used Luna 5u C18 (2) 100A of size 0.25m *4.6mm with flow rate of 1.0 mL/min using 260nm as detector. The describe method was linear over concentration range of 10-50 ppm for assay of Dexketoprofen Trometamol. The retention time of Dexketoprofen Trometamol was found to be 4.31. Result of analysis was validated statistically. Both the method shows good reproducibility and recovery with less than 1%. All the test above mentioned studies were found to be in acceptance criteria. The method was found to be rapid, specific, precise and accurate and can be successfully applied for the routine analysis of Dexketoprofen Trometamol bulk and marketed dosage form.

KEY WORDS: Dexketoprofen Trometamol, HPLC and UV.

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INTRODUCTION

Dexketoprofen Trometamol, 2-amino-2-(hydroxymethyl)-1, 3-propanediol (s)-3-benzoyl-alpha-methylbenzeneacetate; L-Ketoprofen trometamol is a non-steroidal anti-inflammatory drug. The drug is available in the tablet dosage form and it is non-compendial. As to our best knowledge, no UV spectrophotometric or HPLC method has been described for the determination of this drug. Hence, the aim of the present investigations is to develop a simpler, rapid and cost effective analytical method for determination of Dexketoprofen Trometamol in bulk and drug in tablet dosage form suitable for routine quality control analysis.

Reasons for the Development of Newer Method of Drugs Analysis are:

- The drug or drug combination may not be official in any Pharmacopoeias.
- A proper analytical procedure for the drug may not be available in the literature due to patent regulations.
- Analytical methods may not be available for the drug in the form of a formulation due to the interference caused by the formulation excipients.
- Analytical methods for the quantitation of the drug in biological fluids may not be available.
- Analytical methods for a drug in combination with other drugs may not be available.
- The existing analytical procedures may require expensive reagents and solvents. It may also involve cumbersome extraction and separation procedures and these may not be reliable.

Method validation is the process used to confirm that the analytical procedure employed for a specific test is suitable for its intended use. Results from method validation can be used to judge the quality, reliability and consistency of analytical results; it is an integral part of any good analytical practice.

Analytical Methods Need to be Validated or Revalidated:

- Before their introduction into routine use;
- Whenever the conditions change for which the method has been validated (e.g., an instrument with different characteristics or samples with a different matrix); and.
- Whenever the method is changed and the change is outside the original scope of the method.

Advantages of Analytical Method Validation

- The biggest advantage of method validation is that it builds a degree of confidence, not only for the developer but also to the user.
- Although the validation exercise may appear costly and time consuming, it results inexpensive, eliminates frustrating repetitions and leads to better time management in the end.
- Minor changes in the conditions such as reagent supplier or grade, analytical setup are unavoidable due to obvious reasons but the method validation absorbs the shock of such conditions and pays for more than invested on the process.

MATERIALS AND METHODS

UV Spectroscopy

Materials

Dexketoprofen Trometamol API was supplied by Emcure Pharmaceutical Limited. Pune. The commercial fixed dosed product containing 25 mcg Dexketoprofen Trometamol and placebo tablets of Dexketoprofen Trometamol were used from Emcure Pharma (Brand name: INFEN). While UV-Spectrophptometric instrument, Analytical balance, pH mater, Hot air oven and Sonicator used here where of Shimadzu UV 1800, Ohaus USA (0.1 to 200gm), MAC (MSW 552), MAC (SPD 229), Toshcon ultrasonic cleaner respectively.

Methods

Selection of solvent[1]: Solubility of the drug was checked in solvent like water, methanol, acetone, acetonitrile, dimethylsulphoxide, dimethylformamide, dimethyl amine etc. and UV spectra of drugs in this solution were recorded. Absorbance of drug exhibited distinct λ_{max} in water. Hence water was selected as solvent for further studies.

Selection of wavelength[2]: A standard solution of Dexketoprofen Trometamol was prepared in water. From standard solution µg/mL was prepared. This solution was scanned in UV region and their spectrum is shown in Figure 1.

Preparation of stock solution (for pure drug)[3]: Weight accurately 100mg of Dexketoprofen Trometamol, transferred to a 100mL volumetric flask, extracted and made up to volume with water and filtered. Take 10 mL from that solution to 100mL volumetric flask and make up the volume to 100mL with distilled water (stock solution). From the stock solution different concentration of Dexketoprofen Trometamol (2-12 µg/mL), were prepared and scanned in UV region at 260 nm[3]. Because at 260 nm, good linearity was observed and hence this wavelength was fixed for their estimation[4].

Preparation of stock solution (For Formulation) : Twenty tablets, each containing 25 mg of Dexketoprofen Trometamol ware weighted and average weight was calculated. Quantity equivalent to 100 mg of Dexketoprofen Trometamol were weighted, transferred to a 100mL volumetric flask, extracted and made up to volume with water and filtered. Take 10 mL from that solution to 100mL volumetric flask and make up the volume up to 100mL with distilled water. From this solution, suitable aliquots were prepared, scanned in UV region and absorbance were noted at selected wavelengths. From the stock solution take 0.4mL in to 10mL volumetric flask and diluted to 10 mL with distilled water[5]

The amount of Dexketoprofen Trometamol was calculated by using standard statistical method i.e. by putting the value in calibration curve[6].

Linearity and Range: Dexketoprofen Trometamol was found to be linear in the concentration range of 2-12 µg/mL. The absorbances of these solutions were noted at selected wavelengths, 260nm. Calibration curve was plotted using mean concentration v/s absorbance. At a wavelength of 260nm co-efficient value was found to be 0.9997, Figure-2[7].

Precision: Precision studies were performed by preparing the standards six times and measuring the absorbencies of drugs at 260nm. Low %RSD shows that the method has good precision[8].
Intraday precision was performed by standard six times and measuring the absorbencies of drugs at 260nm at same day with time interval[9].
Inter day precision was performed by standard six times and measuring the absorbencies of drugs at 260nm at different day interval[10].

Recovery studies: In order to ensure the stability reliability of proposed method, recovery studies were carried out. To an equivalent quality of formulation powder, a known quantity of standard Dexketoprofen Trometamol was added at 50%, 100% and 150% level and the contents were re-analyzed by the proposed method. The % recovery and %RSD were calculated, Recovery was calculated by using the formula, Table-1 [11,12,13].

High Performance Liquid Chromatography

Instrument

Shimadzu HPLC (model no: SPDM – 20 LC 20 AD)

- UV-Visible detector with isocratic pump
- Column : Luna C_{18}
- Length :250 cm
- Particle size : 5 µm
- Flow rate : 1mL/min
- Injector : Hamilton syringe with 20 µl capacity
- Software : LC lab solution

Materials

Dexketoprofen Trometamol API was supplied by Emcure Pharmaceutical Ltd. Pune. The commercial fixed dosed product containing 25 mcg Dexketoprofen Trometamol and placebo tablets of Dexketoprofen Trometamol were used from Emcure Pharma. (Brand name: INFEN). Disodium Hydrogen Orthophosphate and Potassium Dihydrogen Orthophosphate obtained from Shulabh Chem. (supplied by Suvidhinath Lab. Baroda)

Reagents

Milli-Q water**,** Acetonitrile (HPLC grade), Methanol (HPLC grade) supplied by Durga Lab. Baroda)

Methods

Preparation of solutions:
Preparation of phosphate buffer pH 6.8: Phosphate buffer pH 6.8 was prepared by mixed dissolve 28.80 g of disodium hydrogen orthophosphate and 11.45 g of potassium dihydrogen orthophosphate in sufficient milli Q water to produce 1000 mL. (as per the IP specification) [14, 15]
Preparation of mobile phase / diluents[16,17]: The mixture of Methanol (HPLC) and phosphate buffer with pH 6.8 was prepared in ratio of 70:30.

Stock solution for dexketoprofen trometamol (100 µg/mL) [18]: An accurately weighed quantity of 100mg Dexketoprofen Trometamol was transferred into 100 mL volumetric flask. About 50 mL of diluents was added and sonicate to dissolve, then made up to the mark with diluents. Take 10 mL from that and transfer to 100mL volumetric flask to make up the volume up to the mark with diluents. From this stock solution different aliquots were prepared.

RP-HPLC method development and optimization[19]: The standard solution of Dexketoprofen Trometamol was used for method development trials to optimize the method for determination of Dexketoprofen Trometamol.

Selection of detection wavelength[20]: As per the selection of UV method development, Spectra Shown in the Figure 1.

Selection of column: From the reference from method of Ketoprofen API in BP Waters Spherisorb C18 column was selected [21].

Selection of mobile phase: Optimization can be started only after a reasonable chromatogram has been obtained. A reasonable chromatogram means that more or less symmetrical peak on the chromatogram detects all the compounds. By slight change of the mobile phase composition, the position of the peaks can be predicted within the range of investigated changes. An optimized chromatogram is the one in which all the peaks are symmetrical and are well separated in less run time[22].

The mobile phase was selected on the basis of best separation, peak purity index, peak symmetry, theoretical plate etc. So, numbers of trial were taken. After number of trial Phosphate buffer (pH 6.8): Methanol (30:70v/v) was selected[23].

Selection of oven temperature: Oven temperature is keep ambient [24].

Standard curve: Prepared 10 ppm dilution from the standard stock solution and injected to HPLC. Same prepared 20, 30, 40 & 50 ppm dilution respectively and prepared the concentration V/S area plot. (Figure-4)[25]

Sample preparation (Dexketoprofen Trometamol Tablet): Twenty tablets were weighted and powdered which were transferred equivalently to 100mg of Dexketoprofen Trometamol in to 100mL vol. Flask. Add 50mL of diluents and sonicate for 20mins made up the volume up to mark with diluents and mixed. Resulting solution was filtered through 0.45µm filter paper. Withdraw 10mL of sample and transfer it into 100mL volumetric flask and made volume up to mark with diluents. From this stock solution different aliquots were prepared[26].

Validation approach[27]: Validation of analytical method shall be done to establish by laboratory studies, that the performance of the method meet the requirement for the intended analytical application.

Specificity[28,29]: Specificity of an analytical method is ability to measure specifically the analyte of interest without interferences from blank and placebo.

Check for interference from blank: Diluent was used as blank. Standard and sample were prepared as per test procedure. Check for the interference of blank and peaks with the analyte peak and calculate % interference of blank peaks interferes with analyte peak against the standard peak area.

Linearity and range[30]: The linearity was determined at five levels over the range of 50% to 150% of sample concentration (Table 2). Inject Solvent mixture as blank, standard solution as per test procedure and above linearity solution preparations at each level in duplicate. Calculate mean area at each level and plot a graph of mean area (y-axis) versus concentration in % (x-axis). Calculate and record value of correlation co-efficient (r), y-intercept, slope of regression line and residual sum of squares.

Precision: Method precision for assay was established by determining the assay of six sample preparations under same conditions. Six replicates of sample were prepared at sample concentration by one analyst and analyzed on same day[31]. Intraday precision was performed by standard six times and measuring the area of drugs at same day with time interval. Inter day precision was performed by standard six times and measuring the area of drugs at different day interval[32].

Accuracy (By recovery study)[33]: Accuracy was determined over the range of 50% to 150% of the sample concentration. Calculated amount of Dexketoprofen Trometamol API was added in placebo to attain 50%, 100% and 150% of sample concentration. (Table 3). Amount as shown above was transferred into 50 mL volumetric flask and made up to the mark with diluent. The volumetric flask was sonicated for 10 minutes with intermittent shaking. Each sample was prepared in triplicate at each level and injected. The chromatograms were recorded and from the peak area of drug, % recovery was calculated from regression equation as shown in Table 4

Robustness[34]: The following parameters were changed one by one and their effect was observed on system suitability.

a) Flow rate of mobile phase (± 20%) to 0.8 mL/min, 1mL/min and 1.2 mL/min.

b) pH (± 0.2 absolute) to 6.6, 6.8 and 7.0

System suitability: System suitability was performed and calculated at the start of study of each validation parameter. The values of system suitability results obtained during the entire study were recorded[35]. Procedure is as follows:

- Injected diluent as a blank and recorded chromatogram.
- Injected standard preparation for five replicate, recorded the chromatogram and % Relative Standard Deviation was calculated from regression equation (Figure- 4).

RESULTS AND DISCUSSION

UV Spectroscopic Method

Estimation of Dexketoprofen Trometamol was achieved by simple mathematical equation method using Shimadzu double beam UV-Visible Spectrophotometer. Stock solution of Dexketoprofen Trometamol was prepared in distilled water. The normal spectrum of

Dexketoprofen Trometamol was recorded in water. Linearity was checked in different concentrations. The calibration curves were obtained for Dexketoprofen Trometamol in the range of 2-12 µg/mL. The Regression value of Dexketoprofen Trometamol at 260 nm was found to be 0.9990.

The recovery study was carried out to ensure the reproducibility and reliability of the method by adding known amount of standard drug solution and analysis was carried out as per developed procedure.

RP-HPLC Method

RP-HPLC method developed for estimation of Dexketoprofen Trometamol Tablet Dose. Developed RP-HPLC method was validated according to ICH guideline.

RP-HPLC method has shown adequate separation for Dexketoprofen Trometamol. Separation was achieved on a Luna C_8, 250 mm x 0.5, 5 µm column at 30°C temperature by using methanol (70:30 v/v): phosphate buffer (pH 6.8) as a mobile phase at a flow rate of 1.0 mL/min, and UV detection was carried out at 260 nm. (Figure 3)

In the present study the specificity of the method was determined by assessing interference from the placebo & diluents. There were no other co eluting, interfering peaks from excipients, impurities found and the method was specific for estimation of Dexketoprofen Trometamol.

The method was validated in terms of linearity, precision, accuracy, specificity, robustness and solution stability. The linearity of the proposed method was investigated in the range of 10-50 ppm of test concentration (r^2 = 0.9988) for Dexketoprofen Trometamol. Accuracy was determined by recovery study & it was found to be 98.31% w/w - 99.62% w/w for Dexketoprofen Trometamol Tablet. An assay result of tablet dosage form was found to be 99.80% w/w for Dexketoprofen Trometamol (for batch EM300181).

CONCLUSION

All the validation parameters for all the developed methods were studied as per the ICH guidelines. All the methods were found to be simple, accurate, Specific, Selective, Precise and reproducible.

Hence, the methods can be used for routine analysis of both the drugs in their combined solid dosage form.

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TABLES AND FIGURES

Table-1 Recovery study of Dexketoprofen Trometamol

LEVEL	% RECOVERY	
	STANDARD	FORMULATION
50%	103.16%	101.33%
100%	101%	98.62%

Table 2: Preparation of solution for linearity of Dexketoprofen Trometamol

Conc. (ppm) Dexketoprofen Trometamol	Amount taken (mL) Stock of Dexketoprofen Trometamol (100 µg/mL)	Diluted up to (mL)
10	1	100
20	2	100
30	3	100
40	4	100
50	5	100

Table 3: Sample preparations for accuracy

Sample	Dexketoprofen Trometamol (mL)
Level 1 (50%)	15 ppm
Level 2 (100%)	20 ppm
Level 3 (150%)	25 ppm

Table-4 Determination of Accuracy

Dexketoprofen Trometamol %			
Amt. of Sample µg/ml	**Amt. of drug added µg/ml**	**Amt. recovered µg/ml**	**% Recovery**
10	5	14.866 µg/ml	99.10%
10	10	19.66 µg/ml	98.31%
10	15	24.90 µg/ml	99.62%

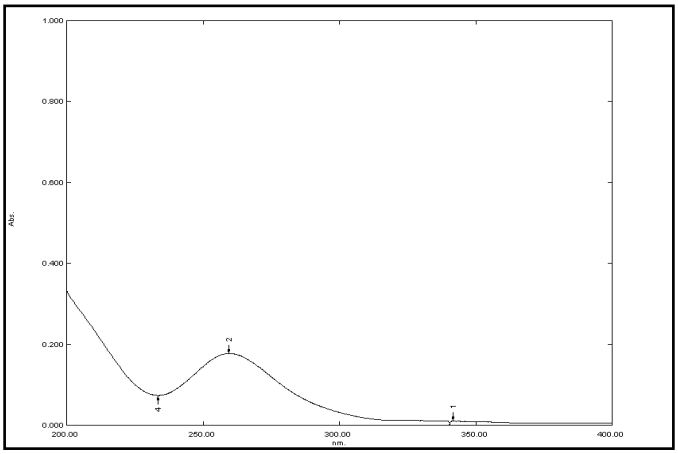

Figure: 1 Determination of maximum wavelength of the Dexketoprofen Trometamol

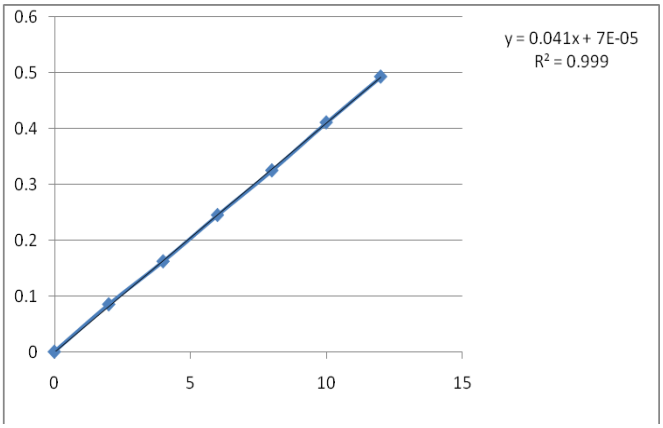

Figure: 2 Calibration curve of the Dexketoprofen Trometamol

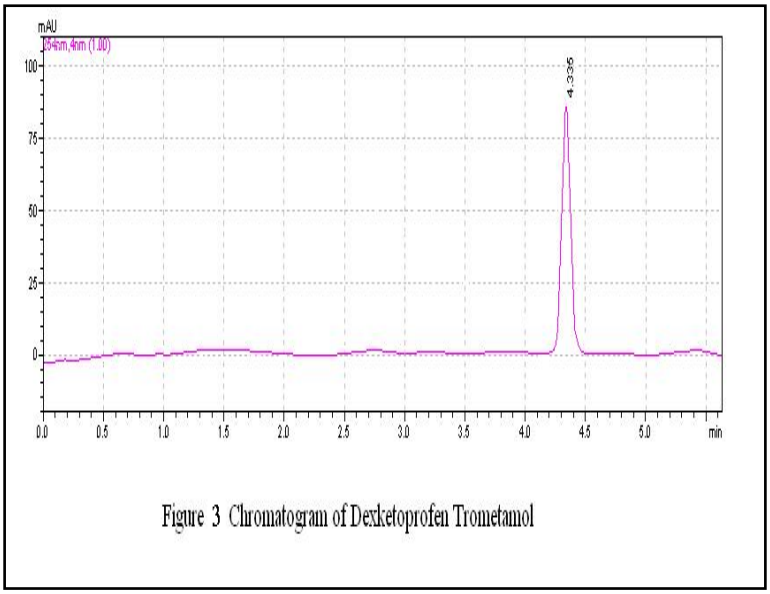

Figure: 3 Chromatogram of Dexketoprofen Trometamol

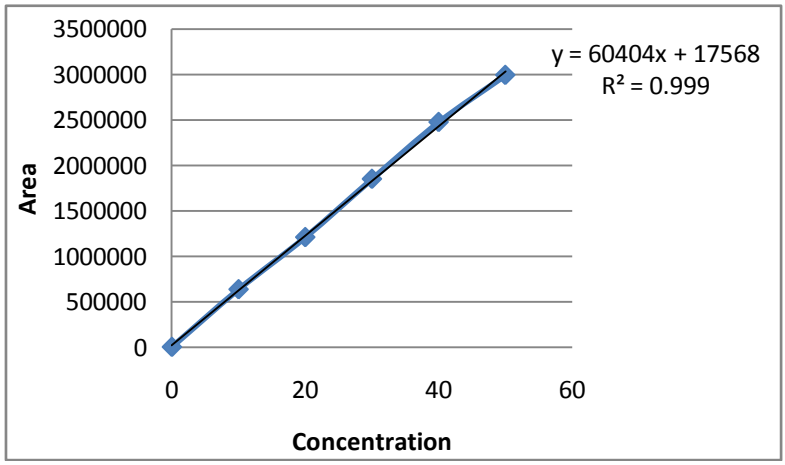

Figure-4 Standard curve of Dexketoprofen Trometamol