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Research Article

DEVELOPMENT AND VALIDATION OF FIRST ORDER DERIVATIVE SPECTROPHOTOMETRIC METHOD FOR SIMULTANEOUS ESTIMATION OF PARACETAMOL AND TAPENTADOL HYDROCHLORIDE IN TABLET DOSAGE FORM

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ABSTRACT:

A simple, precise, accurate and reproducible spectrophotometric method has been developed for Simultaneous estimation of Paracetamol and Tapentadol Hydrochloride by employing first order derivative zero crossing method in 0.1 N Sodium Hydroxide. The first order derivative absorption at 257.1 nm (zero cross point of Paracetamol) was used for quantification of Tapentadol HCl and 289.0 nm (zero cross point of Tapentadol HCl) for quantification of Paracetamol. The linearity was established over the concentration range of 15-35 µg/ml and 3-15 µg/ml for Paracetamol and Tapentadol HCl with correlation coefficient (r^2) of 0.9989 and 0.9993 respectively. The mean % recoveries were found to be in the range of 99.52% – 99.88% and 98.39% – 98.66% for Paracetamol and Tapentadol HCl, respectively. Interday and intraday studies showed repeatability of the method. The method is successfully applied to pharmaceutical formulation, with no interference from excipients as indicated by the recovery study. All validation parameters were within the acceptable range. The proposed method has been validated as per ICH guideline and successfully applied to the simultaneous estimation of Paracetamol (PCM) and Tapentadol HCl (TAP) in their combined Tablet dosage form. The proposed method is recommended for routine analysis since it is rapid, simple, accurate and also sensitive and specific by no heating and no organic solvents are required. Also use of 0.1 N Sodium Hydroxide (NaOH) as a solvent makes it Cost effective and very economical method.

KEY WORDS: Paracetamol (PCM), Tapentadol HCl (TAP), Spectroscopy, First order Derivative, Validation.

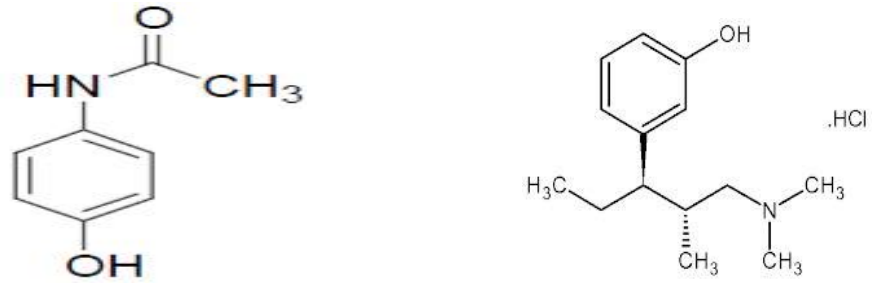
INTRODUCTION:

Paracetamol is 4-hydroxy acetanilide. It is analgesic, antipyretic agent and is the active metabolite of phenacetin, responsible for its analgesic effect by inhibiting COX 2 enzyme. It is a weak prostaglandin inhibitor in peripheral tissues and possesses no significant anti inflammatory effects. It is one of the most important drugs used for the treatment of mild to moderate pain when an anti inflammatory effect is not necessary [1-3].

Tapentadol Hydrochloride is chemically (3-[(1R, 2R)-3-(3-dimethylamino) -1- ethyl -2- methyl propyl] phenol monohydrochloride. Tapentadol is a centrally-acting opioid analgesic is used in the treatment of Acute Pain Management. It belongs to Non-Steroidal Anti Inflammatory Drug (NSAIDs). It is a centrally acting synthetic analgesic. Although its exact mechanism is unknown, analgesic efficacy is thought to be due to be due to µ -opioid agonist activity and the inhibition of norepinephrine reuptake. It is also an agonist of the σ2 receptor, though the function of this orphan receptor remains controversial. The use of PCM and TAP combination therapy for the management of the pain associated with Osteoarthritis (OA) has been recommended to improve efficacy [4, 5].

A Tablet Dosage form containing PCM-325 mg & TAP-50 mg is commercially available. Literature survey revealed the most recent methods for determination of Paracetamol like chromatographic, electrochemical and spectrophotometric techniques are available [6-13]. Tapentadol Hydrochloride is not official in any Pharmacopoeia. Literature review revealed that several analytical techniques for estimation of Tapentadol

Hydrochloride from Various biological Fluids by UPLC, LC/MS/MS, Chiral Chromatography and fluorimetric determination are available [14-19]. However, 1st order derivative spectrophotometric method and RP-HPLC [20] had been reported, for determination of this combination by using methanol as a solvent. This method uses 0.1 N NaOH as a solvent which makes method very cost effective as no costly solvent is used.



(A) Paracetamol (B) Tapentadol Hydrochloride

Figure 1: Chemical structure of (A) PCM and (B) TAP

MATERIALS AND METHODS

Reagents and chemicals

Analytically pure Paracetamol and Tapentadol HCl were used. Tablet of Paracetamol and Tapentadol HCl in combine dosage form, with a 325 mg PCM and 50 mg TAP label claim, manufactured by Glenmark Pharmaceuticals, India were procured from a local pharmacy.

Instruments

The Spectrophotometer used for study is Shimadzu UV/Vis 1800 double beam spectrophotometer with wavelength accuracy (± 0.3 nm), 1 cm matched quartz cells and UV probe 2.35 software was used for all the spectral measurements. Calibrated analytical balance Denver SI234, Germany was used for weighing purpose. All statistical calculations were carried out using Microsoft excel 2010 analytical tool.

Preparation of standard stock solutions

Accurately weighed 100 mg of PCM and TAP standard were transferred to separate 100 ml volumetric flask and dissolved in 50 ml 0.1 N NaOH. The flasks were shaken; sonicated & volume was made up to the mark with 0.1 N NaOH to give solutions containing 1000 µg/ml PCM and 1000 µg/ml TAP.

Selection of Analytical Wavelength

Solutions of PCM and TAP were prepared in 0.1 N NaOH by appropriate dilution and spectrum was recorded between 200-400 nm and all zero order spectrums (D0) were converted to first derivative spectrum (D1) using delta lambda 10 and scaling factor 1.0. The overlain first derivative spectrums of PCM and TAP at different concentration were recorded. The zero crossing point (ZCP) of PCM was found to be 257.1 nm and ZCP of TAP was found to be 289.0 nm **(Figure 2)**.

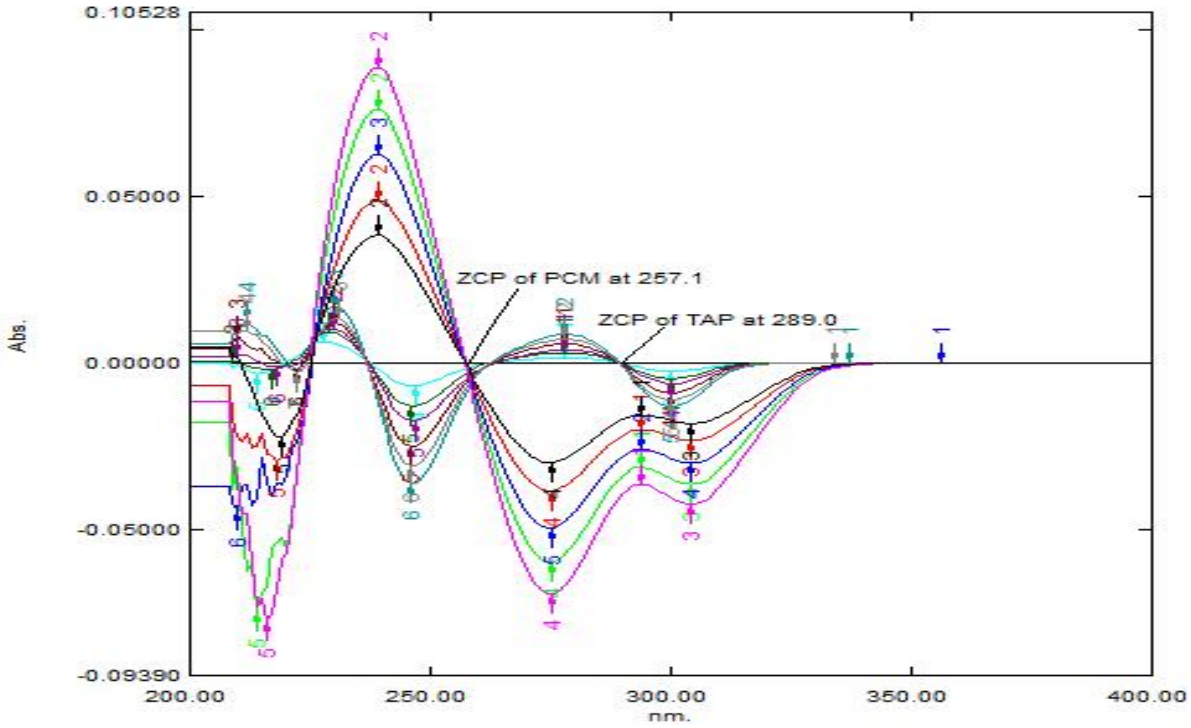


Figure 2: Overlain D^1 spectrum of PCM (15-35 ppm) and TAP (3-15 ppm) in 0.1 N NaOH. ZCP of PCM (257.1 nm), ZCP of TAP (289.0 nm)

Method validation

The proposed method has been extensively validated in terms of specificity, linearity, accuracy, precision, limits of detection (LOD) and quantification (LOQ), robustness and reproducibility.

Specificity

The Drugs were quantified from the taken Pharmaceutical Formulation. The D1 spectrum was recorded by appropriate dilutions and the quantities of drugs were determined.

Linearity

Appropriate volume of aliquot from PCM and TAP standard stock solution was transferred to volumetric flask of 10 ml capacity. The volume was adjusted to the mark with 0.1 N NaOH to give a solution containing 15-35 µg/ml PCM and 3-15 µg/ml TAP. All D1 Spectrum were recorded using above spectrophotometric condition. D1 absorbance at 257.1 nm and 289.0 nm were recorded for PCM and TAP respectively. Calibration curves were constructed by plotting average absorbance versus concentrations for both drugs.

Accuracy

Accuracy was assessed by determination of the recovery of the method by addition of standard drug to the prequantified sample preparation at three different concentration levels 80, 100 and 120%, taking into consideration percentage purity of added bulk drug samples. Each concentration was analyzed three times and average recoveries were measured.

Precision

The intraday and interday precision study of PCM and TAP was carried out by estimating different concentrations of PCM (20, 25, 30 µg/ml) and TAP (6, 9, 12 µg/ml), three times on the same day and on three different days and the results are reported in terms of % RSD.

Detection limit and Quantitation limit

ICH guideline describes several approaches to determine the detection and quantitation limits. These include visual evaluation, signal-to-noise ratio and the use of standard deviation of the response and the slope of the calibration curve. In the present study, the LOD and LOQ were based on the third approach and were calculated according to the 3.3σ/S and 10σ/S criterions, respectively;

Where, **σ** is the standard deviation of y-intercepts of regression lines and

S is the slope of the calibration curve.

Robustness

The sample solution was prepared and then analyzed with change in the typical analytical conditions like stability of analytical solution.

Determination of PCM and TAP from combined Tablet dosage form

Content of Twenty Tablets were weighed accurately. A powder quantity equivalent to 130 mg PCM and 20 mg TAP was accurately weighed and transferred to volumetric flask of 200 ml capacity. 100 ml of 0.1 N NaOH was transferred to this volumetric flask and sonicated for 15 min. The flask was shaken and volume was made up to the mark with 0.1 N NaOH. The above solution was filtered through whatman filter paper (0.45µ). The solution was diluted with the 0.1 N NaOH to give a solution containing 26 µg/ml of PCM and 4 µg/ml of TAP. The resulting solution was analyzed by proposed method. The quantitation was carried out by keeping these values to the straight line equation of calibration curve.

RESULTS & DISCUSSION

For this method, 289.0 nm (Zero crossing point of TAP) and 257.1 nm (zero crossing point of PCM) of first order derivative spectra were selected for the analysis and the linearity range of 15-35 µg/ml & 3-15 µg/ml for PCM and TAP was taken respectively. Straight line equations were obtained from these calibration curves which were shown in figure **(Figure 3 & 4).** The Correlation Coefficients (r^2) for PCM & TAP was found to be 0.9987 & 0.9982 respectively.

Absorption of PCM at ZCP of TAP & absorption of TAP at ZCP of PCM is taken (**Figure 5 & 6**). The % assay was found to be 99.74% for PCM & 98.54% for TAP respectively (**Table 1**). No interference was observed from the Pharmaceutical excipients. For PCM & TAP the percent recovery found is 99.71 & 98.54% respectively **(Table 2)**. The intraday precision and interday precision were expressed in terms of relative standard deviation (RSD). For intraday & interday precision % RSD for PCM & TAP was found to be satisfactory. The inter day precision at three concentration levels (n = 3) on three different days was also evident with a low % RSD providing ruggedness of the method. Hence, the proposed method was evaluated statistically and was validated in terms of linearity, accuracy, precision and ruggedness. The present work provides an accurate and sensitive method for the analysis of PCM and TAP in bulk and tablet formulation **(Table 3)**.

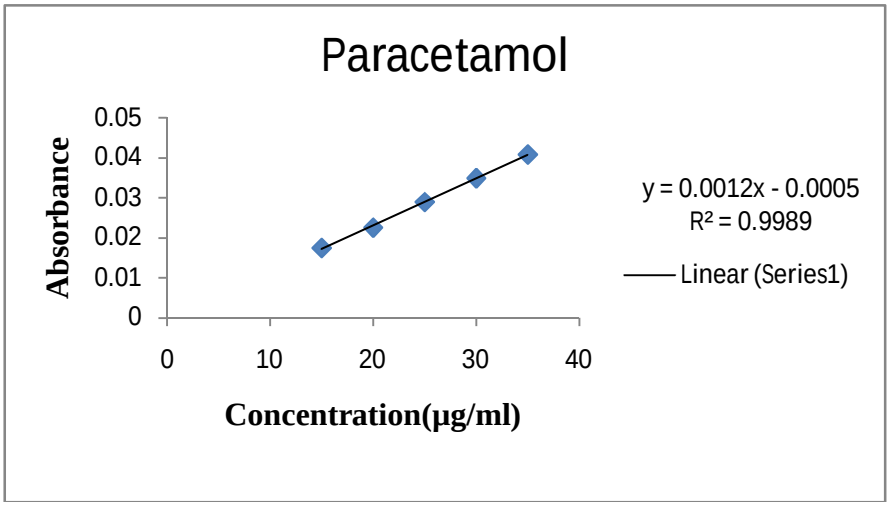


Figure 3: Calibration Curve of Paracetamol

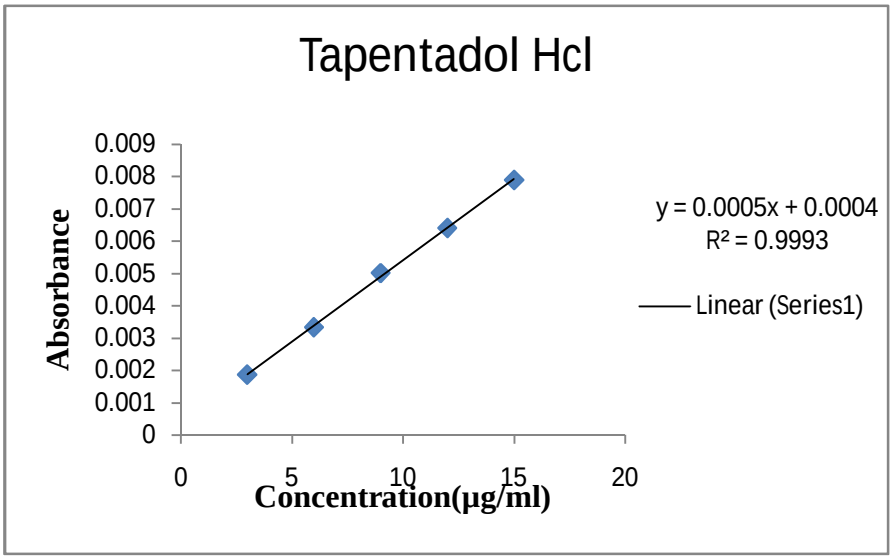


Figure 4: Calibration Curve of Tapentadol HCl

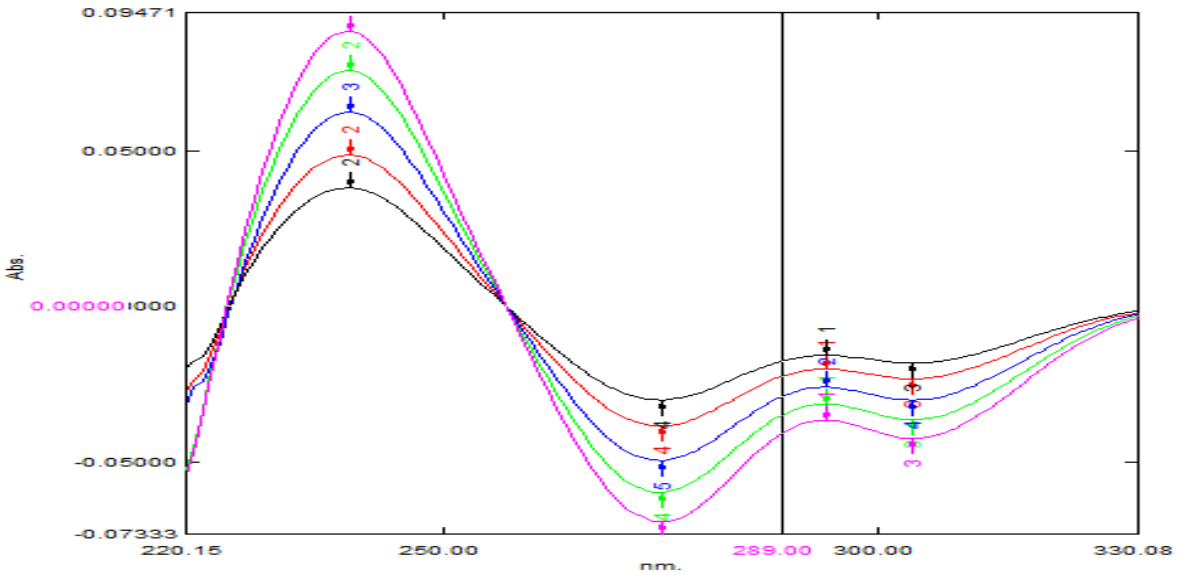


Figure 5: Overlain D^1 spectrum of PCM (15-35 ppm) in 0.1 N NaOH

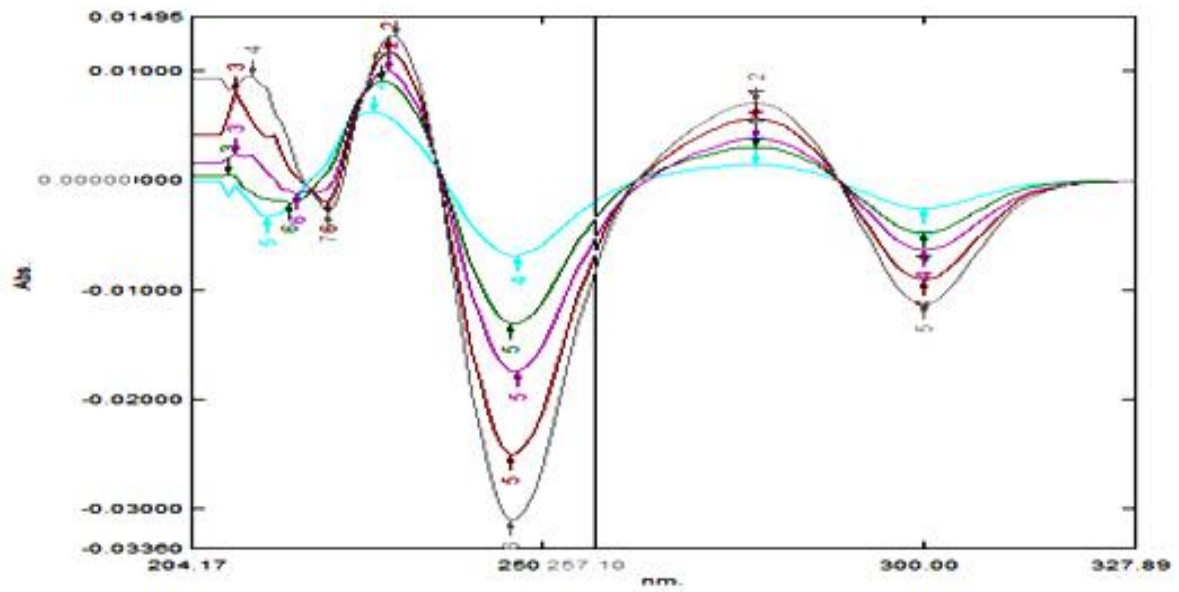


Figure 6: Overlain D^1 spectrum of TAP (3-15 ppm) in 0.1 N NaOH

Table 1: Results of analysis of tablet formulation

Drugs	Label claim (mg)	Amount of drug estimated (mg/tab)	% Label claim ± S.D.	% Recovery
PCM	325	324.36	99.80 ± 0.000169	99.76%
TAP	50	49.56	99.12 ± 0.000039	98.90%

Table 2: Results of recovery studies (tablet)

% Level	Amt. of PCM taken in µg/ml	Amt. of TAP taken in µg/ml	Amt. of Std PCM added in µg/ml	Amt.of Std TAP added in µg/ml	% Recovery (PCM)	% Recovery (TAP)	%RSD PCM	%RSD TAP
80%	26	4.0	20.8	3.2	99.68%	98.86%	0.92%	1.04%
100%	26	4.0	26.0	4.0	99.85%	99.14%	1.04%	1.12%
120%	26	4.0	31.2	4.8	99.76%	98.69%	0.89%	0.96%

Table 3: Results of validation parameters

Parameter	Paracetamol	Tapentadol HCl
Linearity (µg/ml)	15 – 35 µg/ml	3 – 15 µg/ml
Co-relation coefficient(r^2)	0.9989	0.9993
Slope	0.0012	0.0007
Intercept	0.0005	0.0004
LOD (µg/ml)	1.16116	0.18257
LOQ (µg/ml)	3.51868	0.55325
Precision		
Intraday (n=3) Mean ± %RSD	99.74 ± 1.14	99.18 ± 0.93
Interday (n=3) Mean ± % RSD	99.58 ± 1.02	98.86 ± 1.24

CONCLUSION

Based on the results obtained, it is found that the proposed method is accurate, reproducible & economical and can be employed for routine quality control of Paracetamol and Tapentadol HCl in bulk and its dosage form.

ACKNOWLEDGEMENT

The authors are heartly thankful to P.G.Department of Pharmaceutical Sciences, Sardar Patel University (Vallabh Vidyanagar, Gujarat, India) for funding entire project and providing the necessary facilities for research work.

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