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# REVIEW ON COMPARATIVE SCREENING OF VARIOUS ANALYTICAL METHODS FOR CEFIXIME TRIHYDTRATE IN PHARMACEUTICAL DOSAGE FORMS

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## ABSTRACT

Cefixime Trihydrate (CT) is a broad-spectrum, third-generation cephalosporin antibiotic derived semi synthetically from the marine fungus Cephalosporium acremonium with antibacterial activity. As does penicillin, the beta-lactam antibiotic CT inhibits bacterial cell wall synthesis by disrupting peptidoglycan synthesis, resulting in a reduction in bacterial cell wall stability and bacterial cell lysis. Stable in the presence of a variety of beta-lactamases, this agent is more active against gram-negative bacteria and less active against gram-positive bacteria compared to second-generation cephalosporins. It is used in lower respiratory tract infection. It is helpful in acute urinary tract infection, bilary tract infection, sinusitis, acute otitis media, peptic ulcer and many more. Thus, numerous number of research works have been conducted and published to estimate CT because of their biological and pharmacological activity. This review article represents the collection and discussion of various analytical methods available in the literature for the determination of CT in bulk, pharmaceutical dosage forms and biological samples comprising of HPLC, HPTLC, UV-Visible spectroscopic method and hyphenated technique such as LC-MS. This brief review is intended to steer the various analytical methods and recent developments implemented for the analysis of CT content in various dosage forms and in combination with antibiotics, which are indeed being explored for the future analytical study of CT.

**KEYWORDS:** Cefixime Trihydrate, Comparative Screening, Hyphenated Technique, ICH guidelines.

## INTRODUCTION

Cefixime Trihydrate (CT) is a broad-spectrum antibiotic derived semi synthetically from the marine fungus Cephalosporium acremonium with antibacterial activity. CT (Fig 1), an antibiotic, is a third-generation cephalosporin like ceftriaxone and cefotaxime. CT is highly stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins due to the presence of beta-lactamases, may be susceptible to CT. The antibacterial effect of CT results from inhibition of mucopeptide synthesis in the bacterial cell wall.

For use in the treatment of the following infections when caused by susceptible strains of the designated microorganisms: (1) uncomplicated urinary tract infections caused by *Escherichia coli* and *Proteus mirabilis*, (2) otitis media caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella catarrhalis* (most of which are beta-lactamase positive), and *S. pyogenes*, (3) pharyngitis and tonsillitis caused by *S. pyogenes*, (4) acute bronchitis and acute exacerbations of chronic bronchitis caused by *Streptococcus pneumoniae* and *Haemophilus influenza* (beta-lactamase positive and negative strains), and (5) uncomplicated gonorrhea (cervical/urethral) caused by *Neisseria gonorrhoeae* (penicillinase- and non-penicillinase-producing strains).

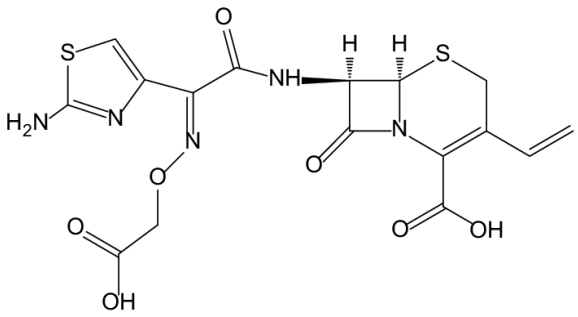


**Fig. 1: Chemical Structure of CT.**

Like all beta-lactam antibiotics, CT binds to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall, causing the inhibition of the third and

last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins; it is possible that CT interferes with an autolysin inhibitor.

The most frequently reported adverse effects, diarrhoea and stool changes, are usually mild to moderate in severity, transient, and mostly occur in the first few days of treatment with CT. Thus, CT is an effective orally active cephalosporin with a relatively long elimination half life permitting a simplified treatment regimen. It is a suitable alternative to cefaclor or amoxycillin in acute otitis media and acute upper and lower respiratory tract infections, and to amoxycillin or co-trimoxazole in acute uncomplicated urinary tract infections.

In the pharmaceutical industry qualitative and quantitative determination of bulk drugs, Active Pharmaceutical Ingredients, raw materials, dosage forms and biological samples are carried out by various analytical methods such as spectroscopy, chromatography and hyphenated techniques. These methods used to ensure the identity, purity, potency and performance of drugs. Analytical method development plays an important role in the development and manufacture of pharmaceuticals.

Various analytical techniques have been developed and employed for content analysis CT in bulk, finished product & in biological matrics and validated as per ICH guidelines to maintain the quality of drug product. Each and every step of a manufacturing process should be controlled to confirm that the finished product meets all the quality control requirements including specifications.[1-4]

**UV SPCTROCOPIC METHOD**

Suddha sattya Dey et al have developed and validated a novel, simple, accurate, sensitive, reproducible, economical and less time consuming spectroscopic method for determination of CT. The solvent used was 0.1N HCL and the absorbance maxima or the λmax was found to be 283.0 nm and 303nm for zero order and first order derivative respectively. This method obeys Beer's Law for the concentration range of 8–16 µg/ml for CT. The proposed method has been validated statistically as per the ICH guidelines for linearity, accuracy, precision, specificity, LOD and LOQ[5].

This study was undertaken by Md. Ahasan Ullah Nayon et al to develop and validate a simple, accurate, precise, reproducible and cost effective UV-Visible spectrophotometric method for the estimation of CT in bulk and pharmaceutical formulation. The solvent used throughout the experiment was the mixer of methanol and water. Absorption maximum (λmax) of the drug was found to be 287 nm. The quantitative determination of the drug was carried out at 287 nm and Beer's law was obeyed in the range of 2-20µg/mL. The recovery values for CT ranged from 99.57% - 100.86%. The percent relative standard deviation (RSD%) of interday precision range was 0.059 – 0.546 % and intraday precision range was 0.102 – 0.299%. The limit of detection and limit of quantification was 0.053 µg/mL and 0.159 µg/mL. The percent relative standard deviation of robustness and ruggedness of the method was 0.258 - 0.365% and complied satisfactorily with ICH guidelines.[6]

Pekamwar S S et al developed simple, accurate, sensitive, economical and reliable first order derivative spectrophotometric method was developed and validated for the estimation of CT and moxifloxacin in pharmaceutical dosage form. Spectrum was obtained by dissolving CT and moxifloxacin in methanol and water (60:40 v/v); wavelength selected was 260 nm for CT and 316 nm for moxifloxacin. The Beer's law was obeyed in the concentration range of 2-12 µg/ml. Results of tablet analysis showed percent relative standard deviation (% RSD) in the range of 0.1576 to 0.2183 for CT and moxifloxacin which indicate repeatability of the method respectively. The method was validated as per ICH guideline and found to be accurate, precise and rugged. It was also validated in terms of linearity, accuracy, precision, and specificity, limit of detection and limit of quantitation.[7]

Mahesh Attimarad et al had performed a research on simultaneous determination of moxifloxacin and CT by first and ratio first derivative ultraviolet spectrophotometry of moxifloxacin HCl and CT. In the first derivative spectrophotometric method varying concentration of moxifloxacin and CT were prepared and scanned in the range of 200 to 400 nm and first derivative spectra were calculated (n = 1). The zero crossing wavelengths 287 nm and 317.9 nm were selected for determination of moxifloxacin and CT, respectively. In the second method the first derivative of ratio spectra was calculated and used for the determination of moxifloxacin and CT by measuring the peak intensity at 359.3 nm and 269.6 nm respectively. Calibration graphs were established in the range of 1–16 µg /mL and 1–15 µg /mL for both the drugs by first and ratio first derivative spectroscopic methods respectively with good correlation coefficients. Average accuracy of assay of moxifloxacin and CT were found to be 100.68% and 98 93%, respectively. Relative standard deviations of both inter and intraday assays were less than 1.8%. Moreover, recovery of moxifloxacin and CT was more than 98.7% and 99.1%, respectively.[8]

Viral Shah et al made work on development and validation for the simultaneous estimation of CT (CEF) and Linezolid (LNZ) by the Q-analysis or absorption ratio UV spectroscopic method and RP-HPLC method. The Q-analysis or absorption ratio method amplitudes at 279 nm (Iso- absorptive point) and 257 nm (λmax of Linezolid) were selected for the assay of CT and Linezolid respectively. The linearity was found in the concentration range of 2-10 µg/ml and 6- 30 µg/ml for CT and linezolid respectively. Reverse Phase High

Performance Liquid Chromatographic method was developed and validated. A Phenomenex Luna C18 column having 250 mm x 4.6 mm, 5µm in isocratic mode, with mobile phase containing HPLC grade Water:Methanol:Acetonitrile (40:30:30% V/V/V) was used. The flow rate was 1 ml/min and effluents were monitored at 279 nm. Chromatogram showed peak of CT at retention time of 1.5 min and Linezolid at retention time of 3.9 min. The present results show that the proposed methods can be successfully used for simultaneous determination of the drug content in marketed formulations.[9]

Abdul Aziz Ramadan et al reported the work on UV-Vis spectroscopic method for the analysis of CT in pure form and pharmaceutical formations through complexation with Cu(II) using acetate-NaOH buffer in mixture water: methanol. Optimal temperature and time for coupling were established at 25±5°C with time ranging from 0 to10 min. The formation of complex, CT: Cu(II ) gives maximum absorbance of the yellow color occurred at λ= 410 nm and the molar absorptivity is 5.12 x 103 L.mol-1.cm-1. The reaction between CT and Cu(II) occurred at a stoichiometric ratio of 1:1. Under optimum conditions Beer's law was obeyed at concentrations ranging from 0.2267 to 22.671µg.mL-1 with correlation coefficients≥0.9995 in all cases with RSD generally less than 4.0%.[10]

Shreya R Shah et al developed simple, accurate, precise, reproducible UV Spectrophotometric methods for the simultaneous estimation of CT and Moxifloxacin in bulk and its synthetic Mixture. First order derivative spectrophotometry method, wavelengths selected for quantitation was 259 nm for CT (zero crossing point for Moxifloxacin) and 380 nm for Moxifloxacin (zero crossing point for CT). In this method linearity was observed in the concentration range of 2-10 µg.mL-1 for CT as well as Moxifloxacin.[11]

Masuma Akter Brishti et al aimed to validate a simple UV-Visible spectrophotometric method for estimating CT in bulk and to produce an accurate, precise, repeatable, and cost-effective method. The pH 7.4 Phosphate buffer was utilized as the solvent throughout the experiment. Beer's law was found to be obeyed in the range of 10-45 µg/mL during the quantitative analysis of the substance at 288 nm. CT recovery values varied from 99.656 percent to 101.825 percent. The inter-day precision range was 0.52-1.02%, and the intraday precision range was 0.57-0.995 percent relative standard deviation (RSD percent). The detection and quantification limits were 0.914 and 3.142 µg/mL, respectively.[12]

Babita et al performed the study to develop simple, precise, accurate, and cost-effective UV visible spectrophotometry method and validation for determination of CT in bulk dosage form by using UV spectrophotometry which was developed according to ICHQ2 (R1) guidelines. The absorption maxima of CT salt were found to be 287 nm. The Validation of method was carried out using Linearity, accuracy, and precision value. The percent relative standard deviation of inter day and intraday precise range (3. 9 – 1.6) & (1.99 – 1.67) respectively shows the method was precise. The recovery of CT salt was found to be 99.8% -100% only.[13]

Md. Ahasan Ullah Nayon et al carried out the to develop and validate a simple, accurate, precise, reproducible and cost effective UV-Visible spectrophotometric method for the estimation of CT in bulk and pharmaceutical formulation. The solvent used throughout the experiment was the mixer of methanol and water. Absorption maximum (λmax) of the drug was found to be 287 nm. Beer's law was obeyed in the range of 2-20µg/mL. The method was shown linear in the mentioned concentrations having line equation y = 0.025x + 0.078 with correlation coefficient of 0.999. The recovery values for CT ranged from 99.57% - 100.86%. The relative standard deviation of six replicates of assay was less than 2%. The percent relative standard deviation (RSD%) of interday precision range was 0.059 – 0.546 % and intraday precision range was 0.102 – 0.299%. Hence, proposed method was precise, accurate and cost effective.[14]

Zeba Mahamad Hanif Gaibu et al has been developed simple, precise, accurate, economical and reliable UV spectrophotometric method for the estimation of CT in bulk and its tablet dosage form. The drug shows maximum absorption (λmax) at 288 nm in methanol and obeys Beer's law in the concentration range of 2-10 µg/ml with correlation coefficient (R2=0.999). The accuracy was found to be 98-99%. Limit of detection (LOD) and limit of quantification (LOQ) were found to be 0.042µg/ml and 0.096µg/ml respectively.[15]

Ethiraj T et al made investigation to apply the hydrotropic solubilization phenomenon for spectroscopic analysis of poorly water-soluble drugs to avoid the use organic solvents which may be costlier, toxic to environment, volatile, and pollutant. A simple ultra violet spectroscopic method was used for the content analysis by diluting the drug CT with various hydrotropic agents. In this study, 20% solutions of sodium salicylate (SS), sodium citrate (SC), sodium acetate (SA), and sodium benzoate (SB) were used as hydrotropes for the analysis of CT. Results and Discussion: The drug CT showed the linearity of .5–2 µg/mL in SS, 5–30 µg/mL in SC, 5–50 µg/mL in SA, and 0.05–0.30 µg/mL in SB solution. Then the proposed methods were validated with respect to accuracy and precision as per International Conference of Harmonization guidelines Q2 (R1). Finally, it was concluded that the all proposed methods were simple, cost-effective, safe to environment, rapid, reproducible, and highly sensitive with SB solution.[16]

Gahandule Mangal has developed a simple, accurate and precise spectroscopic method for simultaneous estimation of CT trihydrate and azithromycin dihydrate in marketed formulation using Q- Absorbance Ratio Method. In this spectroscopic method, 285nm (λmax of CT trihydrate) and 219.40 nm (iso absorptive point for other drugs) were selected for measurement of absorptivity. Both the drugs show linearity in a concentration range of 10-50 µg/ml for CT trihydrate and 2-10 µg/ml respectively. The recovery of CT and azithromycin were found to be 99.84% and 100.76% respectively showing accuracy of the method. The method was validated statistically as per ICH guidelines.[17]

**HPLC METHOD OF ANALYSIS**

Madan Lal Maheshwaria et al made study on determination of CT which has clinical and analytical importance due to its broad spectrum antimicrobial activity and stability. It is for first time that we have developed a new HPLC–DAD method for analysis of imine derivative 3 of CT by using reflux method at 100 C for 50 min without any buffer solution. 2 Thiophenecarboxaldehyde (2TCA) was used first time as a derivatizing reagent for CT drug. Furthermore, separation of three components, i.e. drug (CT), reagent (2TCA) and derivative was carried out using kromasil 100 C-18 (15 mm · 0.46 mm, 5 lm) column with isocratic elution of methanol: 0.1% aqueous formic acid (70:30 v/v) with flow rate of 1 ml min1 at retention time of 1.8, 2.4 and 3.3 min, respectively; while, total run time was 5 min. The method is rapid, simple, very stable and accurate for the separation and determination of imine derivative of CT.[18]

ManchuruVanaja et al developed a new stability indicating RP- HPLC method for CT, Ofloxacin and Linezolid quantification in tablet dosage form. RP-HPLC method was validated with precision, specificity, accuracy, ruggedness, robustness and linearity parameters. Liquid chromatographic conditions are mobile phase A: 0.5M KH2PO4 in HPLC grade water and mobile phase B: Acetonitrile, Agilent make Zorbax SB-C18, 100 x 4.6mm, 5µm, 280 nm, 1.0ml/min, 25 min (gradient program: mobile phase B at 0min 5%, 5min 5%, 10 min 16%, 14 min C16%, 17 min 34%, 20 min 5% and 25 min 5%. This HPLC method can be used to analyze the regular product quality control purpose.[19]

Bashir Elias performed a determination of two generation Cephalosporins (Cefuroxime Axetil and CT Trihydrate) in pharmaceutical dosage forms which was carried out by employing High Performance Liquid Chromatographic using isocratic separation. Separation was performed on an Enable C18 column (250 mm × 4.6 mm, 5.0 µm) using Triethylamine: Methanol: Acetonitrile: Ultra-Pure Water (2:10:20:68 v/v%) as the mobile phase at a flow rate of 1.0 ml/min. The PDA detection wavelength was set at 265 nm. The linearity was observed over a concentration range of 0.1-80 µg/ml for HPLC method (correlation coefficient=0.999). The developed method was used successfully for the determination of Cefuroxime Axetil, CT Trihydrate, in Capsule, Tablet and dry syrup formulations.[20]

Rathinavel G et al presented paper on RP-HPLC method for the simultaneous estimation of CT and cloxacillin in tablets. The process was carried out on C18 column (5 µm, 25 cm x 4.6 mm, i.d) using phosphate buffer (pH 5.0), acetonitrile and methanol in the ratio 80:17: 3 respectively as a mobile phase at a flow rate of 2mL/min. Wavelength was fixed at 225 nm. The retention time of CT and cloxacillin was found to be 5.657 and 6.200 min, respectively. The developed method is rapid and sensitive and it can be used for estimation of combination of these drugs in tablets.[21]

Kavitha rani K et al carried out the work to develop and validate a simple, accurate, precise HPLC method for the estimation of CT and ofloxacin. The chromatographic separation was achieved on a Hypersil BDSC18 column (4.6x250 mm, 5µm particle size). Different mobile phase systems in different proportions were tried. For HPLC method a mobile phase consisting of Methanol and Water (70:30) produced symmetric peak shape with good resolution for both the drugs. Next, the drugs were chromatographed under different flow rates from which a flow rate of 1.0 ml/min was selected. The retention times of CT and ofloxacin were found to be 2.96 min and 4.15 min, respectively. The method was validated for linearity, precision, LOD, LOQ and robustness.The proposed method optimized and validated as per ICH guidelines.[22]

Ajit R Wankhede et al developed and validated a rapid, sensitive and specific RP-HPLC method involving UV detection for the estimation of CT and Cloxacillin in tablet dosage form. The method was validated in terms of linearity, accuracy, precision, specificity, robustness, limit of detection and limit of quantitation. The mobile phase used acetonitrile: tetra-butyl ammonium hydroxide buffer in the ratio of 45:55 and pH adjusted to 4 with orthophosphoric acid. The detection of combined dosage form was carried out at 225 nm at constant flow rate of 1ml/min. Hydrochlorothiazide was used as internal standard. The retention time of CT, Cloxacillin and hydrochlorothiazide were found 5.75 min, 11.90 min and 3.74 min respectively. The proposed method was successfully applied for the quantitative determination of CT and Cloxacillin in tablet dosage form.[23]

Hafiz Muhammad Arshad et al has been developed and validated a simple, selective and rapid reversed phase High Performance Liquid Chromatographic (HPLC) Method for the analysis of CT in bulk material and capsule. The chromatographic system consisted of a LC-10 AT VP pump, SPD-10 AVP UV/visible detector. The Separation was achieved from Bondapak C18 column at ambient temperature with a mobile phase consisting of methanol: buffer solution (sodium dihydrogen

phosphate) [35: 65 v/v, pH=2.75 adjusted with phosphoric acid] at a flow rate of 1ml/min and the retention time was about 6 minutes. The calibration curve was linear over the concentration range of 0.039-20µg/ml (r2 = 0.9998). Therefore, this method could be used as a more convenient and efficient option for the analysis of CT in raw material and capsule dosage form.[24]

Elsadig H K Adam carried out the work to develop simple, accurate, precise and sensitive reverse phase high performance liquid chromatography (RP-HPLC) method for the determination of CT trihydrate and its degraded products. Drug was resolved on a C18 column (waters spherisorb 25 cm × 4.6 mm, 5µm), utilizing mobile phase of sodium dihydrogen phosphate monohydrate (0.1M aqueous) pH adjusted to 2.5 with diluted orthophospharic acid (10 % aqueous) and methanol in a ratio of 3:1 respectively. Mobile phase was delivered at the flow rate of 1.0 ml/min. Ultra violet detection was carried out at 254 nm. Separation was completed within 9.75 minutes. Calibration curve was linear with correlation coefficient (r2) = 0.9996 over a concentration range 10-50 µg/ml. The method was successfully applied to the determination of the decomposed products of CT trihydrate, it can be very useful and an alternate to performing the stability studies.[25]

Zahra talebpour et al had developed a simple, precise, and accurate isocratic liquid chromatography (LC) method for the determination of CT in the presence of its related substances generated from thermal stress in the bulk drug. The chromatographic conditions were comprised of a reversed-phase C18 column (4.6 × 250 mm, 5 µm) with a mobile phase composed of water: acetonitrile (85:15 v/v, with 0.5% formic acid) and ultraviolet detection (UV). Some thermal degradation products were identified using a proposed liquid chromatography-mass spectrometry method. Five peaks (A, B, C, D, and E impurities based on British Pharmacopoeia) were known and a few unknown peaks appeared in the thermal stress solution of CT. The linear regression analysis data for the calibration plot of the LC-UV method showed a good linear relationship in the concentration range 0.9–1000.0 µg $mL^{-1}$. The obtained results shown in the LC-UV proposed method can be conveniently used in a quality control laboratory for routine analysis of CT for the assay and related substances, as well as for the evaluation of stability samples of bulk drugs.[26]

**HPTLC METHODS OF ANALYSIS**

Madhura V Dhoka et al had developed and validated a simple, accurate, precise and rapid high-performance thin-layer chromatographic method for determination of CT Trihydrate and Dicloxacillin Sodium in Bulk and combined pharmaceutical dosage form. The method employed TLC aluminium plates precoated with silica gel 60F254 as the stationary phase and Toluene:Methanol:Triethylamine (4:6:0.7) as mobile phase. Densitometric analysis was carried out at 229 nm. The system was found to give compact spots for CT Trihydrate and Dicloxacillin Sodium at Rf of 0.58 ± 0.03 and 0.80 ± 0.03 respectively. Percent Recovery for CT Trihydrate was 100.75-101.25 and that for Dicloxacillin was 100-101.51. Method was found to be reproducible with % relative standard deviation (%R.S.D) for intra and interday precision.[27]

Smita S Aher performed research on development of simple, precise, accurate and rapid high performance thin layer chromatographic method for the estimation of CTTrihydrate and Ornidazole simultaneously in combined dosage forms. The stationary phase used was precoated silica gel 60F254. The mobile phase used was a mixture of Methanol: Toluene (7:3 v/v) The detection of spots was carried out at 301 nm. The method was validated in terms of linearity, accuracy, precision, LOD and LOQ. The calibration curve was found to be linear between 60 to 160 ng/spot for CT Trihydrate and 150 to 400 ng/spot for Ornidazole and Itopride is used as internal standard. The proposed method can be successfully used to determine the drug content of marketed formulation.[28]

Smita J Pawar developed simple, rapid, reliable and accurate HPTLC method for the quantitative determination of CT and Cloxacillin in bulk and tablets. The drugs were extracted from (Zifi X 200). Various aliquots of this sample solution were spotted automatically by means of Camag (Muttenz; Switzerland) Linomat V sample applicator on Merck HPTLC plates (0.2mm thickness) precoated with silica gel 60 F254 on aluminium sheet as stationary phase prewashed with methanol using n-Butanol: Methanol: Water: Formic acid (8:6:4:0.3v/v/v) as mobile phase. The spots were scanned at 293 and 343 nm for CT and Cloxacillin respectively using Camag TLC scanner. The Rf values of CT and Cloxacillin were found to be 0.28 and 0.45 respectively. Calibration curves were linear in range of 150-600ng per spot. The suitability of this method for quantitative determination of compounds was proved by validation in accordance with requirements of pharmaceutical regulatory standards.[29]

Janhavi Rao et al carried out the work on simultaneous determination of CT and ofloxacin in a bulk drug and pharmaceutical formulations by high performance thin layer chromatographic (HPTLC) method. Chromatographic separation was achieved on aluminum foil plates precoated with silica gel 60GF-254, with n-butanol: ammonia: water: DMSO (8:3:1:2, v/v/v/v) as mobile phase. Detection was performed densitometrically at 297 nm. The RF value of CT and ofloxacin were 0.55 and 0.65, respectively. Accuracy (99.82 % for CT and 99.84 % for ofloxacin) and specificity, in accordance with ICH guidelines were performed. The method is simple, accurate, and rapid and can therefore be used for routine analysis of both drugs in quality control laboratories.[30]

Madhura V Dhoka has developed and validated a simple, accurate, precise and rapid high-performance thin-layer chromatographic method for determination of CTTrihydrate and Erdosteine in Bulk and combined pharmaceutical dosage Form. The method employed TLC aluminium plates precoated with silica gel 60F254 as the stationary phase. The solvent system consisted of Ethyl Acetate:Acetone:Methanol:Water (7.5:2.5:2.5:1.5) as mobile phase. Densitometric analysis was carried out at 235 nm. The system was found to give compact spots for CT Trihydrate and Erdosteine at Rf of 0.35 ± 0.05 and 0.56 ± 0.05 respectively. The linear regression analysis data showed good linear relationship in the concentration range 100-500 ng band-1 and 150-750 ng band-1 for CT Trihydrate and Erdosteine respectively. The method was validated for precision, accuracy, specificity and robustness and has been successfully applied in the analysis of combined capsule dosage form.[31]

Gawande V T developed stability-indicating High Performance Thin-Layer Chromatography (HPTLC) method for simultaneous estimation of CT trihydrate and azithromycin dehydrate. Both the drugs were subjected to different stress conditions recommended by International Conference on Harmonization (ICH) guideline Q1A (R2). Forced degradation was carried out for hydrolytic, oxidative, photolytic, and thermal degradation conditions. CT was susceptible for degradation under all stress conditions showing four degradation products (CI–IV). However, azithromycin formed only one degradation product (AI) under acid hydrolysis. Aluminum plates precoated with silica gel 60F254 were used as the stationary phase while mixture of ethyl acetate–methanol–acetone–toluene–ammonia (1:5:7:0.5:0.5, v/v) was used as mobile phase. Detection wavelength used was 235 nm for CEFI and CI–IV. AZI and AI were detected by post development derivatization, spraying with sulfuric acid–ethanol (1:4, v/v) followed by heating at 100 °C for 5 min. Degradation products were isolated by preparative HPTLC and characterized by MS/MS. The developed method was validated for linearity, precision, accuracy, specificity, and robustness and has been successfully applied in the analysis of these drugs in tablet dosage form.[32]

Devika G S developed and validated simple, rapid, accurate and precise densitometric method for determination of CT trihydrate and ornidazole in combined tablet dosage forms. The separation was achieved on Merck TLC aluminium sheets of silica gel 60 F254 with n butanol-methanol-toluene-ammonia 5:2:1:5 (v/v/v/v) as mobile phase. Densitometric quantification was perfomed at 287nm by reflectance scanning. The RF value of CT trihydrate and ornidazole were found to be 0.51±0.02, 0.36±0.02 respectively. The method was validated with respect to linearity, precision, accuracy, specificity, robustness and ruggedness, in accordance with ICH guidelines. The method proved to be a rapid and cost-effective quality control tool for routine simultaneous analysis of CT trihydrate and ornidazole in the bulk drug and in a tablet dosage formulation.[33]

## CONCLUSION

A lot of research was carried out to analyze content of CT in bulk, in pharmaceutical dosage forms and in biological matrices. The review work provides detailed summary about various analytical methods developed and validated as per ICH guidelines for estimation of CT and combination with other drugs such as moxifloxacin, ornidazole, azithromycin etc. Analytical methods consisting of UV-Visible spectroscopic method, chromatographic method like HPLC and HPTLC were employed for determination of CT in bulk, pharmaceutical dosage forms and biological matrix. From this survey, it is revealed that several analytical methods are developed on HPLC, HPTLC and UV-visible spectrophotometry methods.

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