Int. J. Pharm. Investigation, 2026; 16(4):1377-1383.
https://www.jpionline.org

Review Article

Emerging Analytical Strategies for Screening Hydrochlorothiazide in Fixed Dose Combinations: A Comprehensive Review

Sree Janardhanan Vaithiyanathan*, Nandini Goudar

Department of Pharmaceutical Chemistry, School of Pharmacy, Sri Balaji Vidyapeeth (Deemed to be University), Pondicherry Campus, Pillaiyarkuppam, Puducherry, INDIA.

ABSTRACT

Hydrochlorothiazide (HCTZ) is one of the most widely prescribed thiazide diuretics which is frequently formulated in fixed-dose combinations with angiotensin II receptor blockers, Angiotensin Converting Enzyme (ACE) inhibitors, calcium channel blockers and other anti-hypertensive agents. The extensive clinical use of these combinations necessitates reliable analytical methods for their simultaneous estimation in pharmaceutical dosage forms and biological matrices. The purpose of this study is comprehensively examine previously reported chromatographic and hyphenated analytical methods for HCTZ analysis in combinations with other drugs. The Published literature outlining the analytical techniques for HCTZ based combination dosage forms and its applications were reviewed. Stability indicating Reverse Phase High Performance Liquid Chromatography (RP-HPLC) method remains the most commonly employed techniques for routine quality control and stability testing due to their simplicity, robustness, and regulatory compliances. LC-MS/MS method provides superior sensitive and selective making them suitable for bioanalytical applications such as pharmacokinetics and bioequivalence studies. High Performance Thin Layer Chromatography (HPTLC) offers a cost-effective alternative for pharmaceutical analysis. Recent studies increasingly apply Analytical Quality by Design (AQbD) principles to enhance method optimization. Emerging applications includes impurity profiling, mixed mode chromatography and analysis of novel dosage forms. A reviewed analytical method for HCTZ based fixed dose combination drugs demonstrates excellent accuracy, precision and sensitivity supporting their suitability for reliable pharmaceutical quality control and bioanalytical evaluation. Continuous advancement in chromatographic techniques and AQbD based approaches further strengthen the analytical framework for HCTZ combination drugs.

Keywords Analytical Quality by Design, Antihypertensive drugs, Fixed-dose combinations, Hydrochlorothiazide, LC-MS/MS, Stability-indicating methods.

Correspondence:
Dr. Sree Janardhanan Vaithiyanathan
Department of Pharmaceutical Chemistry, School of Pharmacy, Sri Balaji Vidyapeeth (Deemed to be University), Pondicherry Campus, Pillaiyarkuppam-607402, Puducherry, INDIA.
Email: vsreejana@gmail.com

Received: 16-03-2026;
Revised: 06-05-2026;
Accepted: 29-07-2026.

INTRODUCTION

Hydrochlorothiazide (HCTZ) is a thiazide diuretic that is commonly administered to treat hypertension and related illness such as edema caused by heart failure or renal problems. It acts by inhibiting salt and chloride reabsorption in the kidney's distal convoluted tubules, increasing diuresis and thus lowering blood pressure. HCTZ has been cornerstone of hypertension therapy for decades due to its efficacy, safety profile, and affordable cost (Herman *et al.*, 2023). Combination therapy with HCTZ and other antihypertensives, such as Angiotensin Receptor Blockers (ARBs), Angiotensin II receptor blockers (ACE) inhibitors, and beta blockers, is commonly used to improve blood pressure control, particularly when monotherapy fails to meet therapeutic goals. Clinical data supports up the superiority of combination regimens over monotherapy in lowering systolic and diastolic blood pressure (MacDonald *et al.*, 2017). Combination therapy with HCTZ and other antihypertensives, such as ARBs, ACE inhibitors, and beta blockers, is commonly used to improve blood pressure control, particularly when monotherapy fails to meet therapeutic goals. Clinical data supports up the superiority of combination regimens over monotherapy in lowering systolic and diastolic blood pressure. With the increased use of fixed dose combinations, developing accurate, precise, and robust analytical methodologies has become essential to pharmaceutical quality control and clinical pharmacokinetics evaluation. Chromatographic techniques such as High-Performance Liquid Chromatography (HPLC) and Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) are frequently used for the

OPEN ACCESS

Manuscript TECHNOMEDIA

DOI: 10.5530/ijpi.20260005

simultaneous measurement of HCTZ with co-formulated medicines in tablet and plasma, resulting in high sensitivity and specificity (Liu *et al*., 2007). Furthermore, emerging approaches combine current validation strategies and environmentally friendly consideration in order to meet regulatory requirements and ensure environmental sustainability (Al-Asmar *et al*., 2025). A chemometric design (central composite design) was used to optimized parameters such as mobile phase composition and flow rate. Herby boosting separation and analytical efficiency. The proven method is appropriate for bioavailability and pharmacokinetic studies in clinical and pharmaceutical research (Ganna *et al*., 2022). Precise therapeutic monitoring, impurity profiling, stability studies and pharmacokinetic investigation in both research and clinical contexts.

Importance of Combination Therapy

Fixed-dose combinations of ARBs with HCTZ have demonstrated greater efficacy in lowering systolic and diastolic blood pressure than ARB monotherapy, with similar rates of adverse events, indicating that low-dose HCTZ adds significant antihypertensive benefit without compromising tolerability (Ma *et al*., 2021). Guidelines and clinical data underline the justification for combining drugs with different mechanisms, such as renin-angiotensin system blockers and diuretics, to improve blood pressure control while minimizing side effects. When combined with an ACE inhibitor or ARB, diuretic-induced hypokalaemia can be reduced (Gradman, 2010).

Triple combinations of ARBs, calcium channel blockers, an HCTZ have resulted in significantly greater blood pressure reductions and higher rates of target achievement compared to dual therapies, demonstrating the benefits of multi-mechanism regimens in patients with more severe or difficult-to-control high blood pressure. Single pill fixed dose combinations enhance adherence and simplify drugs, which can lead to sustained 24-hr blood pressure management and better overall clinical results than numerous independent drugs or monotherapy approaches (Volpe and Tocci, 2012). The Central Drug Standard Control Organization (CDSCO)-approved fixed-dose combinations of HTCZ are listed in Table 1 (Central Drugs Standard Control Organization [CDSCO]).

METHODOLOGY

From an analytical and quality control perspective, robust, stability-indicating analytical methods capable of the reliable, precise, and validated simultaneous estimation of HCTZ with co-formulated drugs in both pharmaceutical dosage forms and biological matrices are essential to ensure the assay accuracy, content uniformity, impurity profiling, and stability evaluation of combination products, especially given HCTZ's susceptibility to degradation under hydrolytic, oxidative, and photolytic conditions, which mandates the assurance of product quality and safety throughout the shelf life (Bakshi and Singh, 2002). Variations in physicochemical parameters, such as polarity, pKa, and UV absorption characteristics, worsen analytical problems in multi-component compositions, needing optimal chromatographic separation and selective detection (Blessy *et al*., 2014). Table 2. provides an overview of the various analytical methods reported in the literature for the simultaneous estimation of Hydrochlorothiazide (HCTZ) in combined dosage formulations.

DISCUSSION AND SUMMARY

HCTZ is a commonly prescribed thiazide diuretics that is frequently combined with antihypertensive agent such as ARBs (telmisartan, losartan, valsartan etc), ACE inhibitors (ramipril, lisinopril) calcium channel blockers (amlodipine) and renin inhibitors (aliskiren) in view of its widespread clinical use, pharmaceutical research has focused on developing reliable, sensitive and robust analytical method for determining HCTZ in conjunction with co-administered drugs. The reviewed research article shows considerable advancements in chromatographic and hyphenated analytical techniques for pharmaceutical dosage forms as well as biological matrices. Traditional RP-HPLC as well as HPTLC procedures are still frequently used for routine quality control of combined dosage forms because they are simple, relatively inexpensive and have acceptable precision and accuracy. Several methods including C18 columns isocratic elution UV detection (235-280 nm and internal standards like methylparaben, have demonstrated excellent linearity, low relative standard deviation (<2%) and significant recovery, making them suitable for formulation analysis and content uniformity testing. In contrast-MS/MS - based approaches are widespread in bioanalytical applications, particularly for pharmacokinetics bioequivalence and drug - drug interaction studies. these approaches provide superior sensitivity, selectivity and lower limits of quantification often in the ng/mL or sub-ng/mL range albeit using small plasma volume (≈100 µL). Both liquid - liquid and solid phase extraction technique were used successfully incorporating isotope labelled or structurally related internal standards increasing methods robustness. A significant breakthrough noted by various studies is the rising emphasis on stability - indicating approaches. The tandem application of photodiode array and mass spectroscopy improved peak purity evaluation and structural elucidation of degradation products, including unidentified impurity species resulting from excipient - drug interaction. Further, the use of analytical Quality by Design (AQbD) concepts constituents an evaluation from traditional one- factor - at -a time technique. AQbD- based methodologies improved their robust-ness, regulatory flexibility and lifecycle's reliability by incorporating Design of Experiments (DoE), risk assessment and design space establishment. An overview of the conceptual framework of analytical approaches for HCTZ in fixed-dose combinations is depicted in Figure 1.

These methodologies were effectively used to both traditional formulations and emerging technologies, such as 3D- printed pharmaceutical dosage forms, proving adaptability to innovative drug delivery system. Overall, the data highlight the progression of analytical approaches forms simple routine evaluation to highly sophisticate, stability- indicating, and regulatory - compliant techniques they can support both product developed and clinical research.

Table 1: List of fixed-dose combinations of HCTZ approved in CDSCO.

Combination	Approved Year	Medication class com bination	Treatment for
HCTZ+Benazepril	2004	Angiotensin-converting enzyme inhibitor (ACEI)+ Angiotensin-II receptor blocker+Thiazide	Mild to moderate hypertension
HCTZ+Captopril	1997		Heart Failure, Raised blood pressure
HCTZ +Enalapril	2001		Heart Failure, Raised blood pressure
HCTZ +Fosinopril	2004		Raised blood pressure
HCTZ +Lisinopril	2002		Heart Failure, Raised blood pressure
HCTZ +Moexipril	2007		Raised blood pressure
HCTZ +Quinapril	2005		Raised blood pressure
HCTZ +Candesartan	2012		Raised blood pressure
HCTZ +Irbesartan	2012		Raised blood pressure
HCTZ +Losartan	2010		Raised blood pressure
HCTZ +Olmesartan	2016		Raised blood pressure
HCTZ +Telmisartan	2014		Raised blood pressure
HCTZ +Valsartan	2012		Raised blood pressure
HCTZ +Bisoprolol	2000	β-Blocker+Thiazide	Raised blood pressure
HCTZ +Metoprolol	2004		Raised blood pressure
HCTZ +Amiloride	1987	Potassium-sparing diuretic thiazide	Raised blood pressure
HCTZ +Triamterene	1987		For the management of fluid retention (edema) or Raised blood pressure (hypertension)
HCTZ +Spironolactone	1979	Mineralocorticoid receptor antagonist+Thiazide	Raised blood pressure
HCTZ +Olmesartan +Amlodipine	2016	Angiotensin-II receptor blockers calcium channel blockers+Thiazide	Raised blood pressure
HCTZ+Valsartan+Amlodipine	2013		Raised blood pressure
HCTZ+Candesartan Cilexetil	03.01.2002	Angiotensin-II receptor blocker+ Thiazide	Essential hypertension (not for initial therapy)
HCTZ +Losartan Potassium	08.06.1999	Angiotensin-II receptor blocker or ACEI+Thiazide	For treatment of mild to moderate hypertension
HCTZ +Telmisartan IP	14.05.2013	ACEI or angiotensin-II receptor blockers+ Thiazide	Use as adjunct medication to manage high blood pressure
HCTZ+Amlodipine Besylate	23.11.2011	Potassium-sparing diuretic thiazide	For treatment of hypertension in patients who are not controlled
HCTZ+Ramipril	26.08.1996	ACEI+ Thiazide	Mild to moderate hypertension in patients
HCTZ +Benazapril HCL	21.05.1998	ACEI+ Thiazide	Mild to moderate hypertension only
HCTZ +Lisinopril	23.11.1995	ACEI+ Thiazide	Raised blood pressure

Table 2: Overview of the various analytical methods reported in the literature for the simultaneous estimation of hydrochlorothiazide (HCTZ) in combined dosage formulations

Sl. No.	Drug Estimated	Technique	Description of method	Application	Ref
1.	Telmisartan+HCTZ	Stability indicating RP-LC with internal standard	C18 (25 cm) Column 50 mM ammonium acetate buffer (pH 5.5) and acetonitrile (70:30 v/v) mobile phase with flow rate of 1.0 mL/min detection at 260 nm column temperature of 30°C.	Applied for assay content and quality control	(Rane *et al*., 2008)
2.	Losartan +HCTZ	HPLC-ESI-MS/MS (Negative ion mode, MRM)	Human plasma using liquid-liquid extraction followed by HPLC-ESI-MS/MS in negative ion MRM mode, with valsartan and chlorthalidone as internal standards.	Applied for bioequivalence studies.	(Salvadori *et al*., 2009)
3.	Valsartan+HCTZ	HPTLC with UV detection	Precoated silica gel $60F_{254}$ as the stationary phase. The mobile phase consisted of chloroform: methanol: toluene: glacial acetic acid (6:2:1:0.1v/v/v/v) Densitometric detection was carried out at 260 nm.	Applied for assay content and quality control	(Shah *et al*., 2009)
4.	Irbesartan+ HCTZ	Stability-indicating RP-LC with internal standard.	C18 (25 cm) column, 50 mM ammonium acetate buffer (pH 5.5) and acetonitrile (70:30 v/v) mobile phase with flow rate of 1.5 mL/min. Detection at 235 nm, column temperature of 30°C and Methylparaben internal standard.	Applicable for assay, forced degradation, and routine quality control	(Rane *et al*., 2010)
5.	Candesartan cilexetil+ HCTZ	LC-MS/MS (Negative ion mode) with Liquid-Liquid Extraction	Sample preparation involved liquid-liquid extraction using 100µL Human plasma, followed by LC separation and tandem mass spectrometric detection in negative ion mode; run time of 2.5 min, calibration ranges of 1-160 ng/mL for candesartan cilexetil and 2-160ng/mL for HCTZ.	Applied for pharmacokinetic studies	(Bharathi *et al*., 2012)
6.	Ramipril +HCTZ	LC-MS/MS with ESI (Positive and Negative modes) using LLE	Human plasma using liquid-liquid extraction with methyltert-butyl ether dichloromethane (85:15). Chromatographic separation was achieved on an enable C18G column (150x4.6 mm, 5 µm) using methanol 1:0.1% formic acid in water (85:15) at a flow rate of 0.5 mL/min. Detection was performed by triple quadrupole MS in MRM mode with positive ionization for ramipril and negative ionization for HCTZ using carbamazepine as internal standard.	Applied for pharmacokinetic studies	(Patel *et al*., 2014)
7.	Aliskiren +HCTZ	Stability indicating RP-HPLC	Phenyl column, 0.030 M ammonium acetate-acetonitrile (60:40 v/v) mobile phase with flow rate of 0.40 mL/min and detection at 280 nm.	Applied for assay content uniformity and quality control	(Karvelis *et al*., 2014)
8.	Lisinopril+HCTZ	LC-MS/MS (Negative ion mode, MRM)	Human plasma using solid phase extraction was Water Oasis HLB cartridge, followed by chromatographic separation on a Hypersil Gold C18 (50x3.0 mm, 5 µm) column. The mobile phase consisted of acetonitrile and 5.0mM ammonium for mate (pH 4.5) in the ratio 85:15v/v. Detection was performed using tandem mass spectrometry in multiple reaction monitoring mode with labeled internal standards.	Applied to pharmacokinetic studies.	(Shah *et al*., 2017)

Sl. No.	Drug Estimated	Technique	Description of method	Application	Ref
9.	Amlodipine+Valsartan+ HCTZ	LC-MS/MS with Solid Phase Extraction (SPE)	In human plasma using solid phase extraction on Qasis HLB cartridges (100 µL plasma) Chromatographic separation was achieved on a chromolith RP 18e (100X4.6mm) column under isocratic condition with a total run time of 2.5 min. Detection was performed by tandem mass spectrometry using deuterated internal standard.	Applied to a bioequivalence study	(Shah *et al*., 2009)
10.	Candesartan +HCTZ	HPLC method	Hypersil BDS C18 column (150x4.6x5µm) using mobile phase consisting of phosphate buffer pH 5.4 and acetonitrile (65:35) at flow 1.0 mL/min Detection was carried out at 232nm.	Applied for quality control method.	(Gaurkhede and Chandewar, 2018)
11.	Telmisartan and HCTZ impurities	RP-HPLC(Gradient) with Analytical QbD	Intersil ODS-3V column(150x4.6 mm, 3.5 µm), gradient elution with 0.02M KH_2PO_4(pH 3.5) and water: Acetonitrile (100:900v/v), flow 1 mL/min, 40°C detection at 230 nm. Design of Experiments (DoE) used to identify critical quality attributes and establish method design space.	Applied to forced degradation studies.	(Palakurthi *et al*., 2020)
12.	Fimasartan, fimasartan-amide, amlodipine+ HCTZ	LC-MS/MS	Analysing rate plasma with an Agilent 6470 triple-quadrupole LC-MS/MS instrument. Chromatographic separation was achieved using a Synergi Polar RP column (150x4.6 mm, 4 µm) using an isocratic mobile phase of water acetonitrile (30:70 v/v) containing 0.1% formic acid at a flow rate of 0.20 mL/min. Detection was carried out in Multiple Reaction Monitoring (MRM) mode.	Applied to pharmacokinetic inter action and toxicokinetic studies of triple combination antihypertensive therapy and evaluation of *Panax ginseng* extract effects	(Jeon *et al*., 2022)
13.	losartan potassium and HCTZ	RP-HPLC (Stability-indicating, Analytical QbD)	The X-Bridge C18 column (150x4.6mm,3.5 µm) used a gradient elution of 0.3%formic acid (A) and acetonitrile: methanol 80:20 (B). Flow 1.3 mL/min, 40°C, injection 10µL. Method development followed AQbD principles: ATP definition, bibliographic survey, screening with Plackett-Burman (11 factors, 2 levels), optimization with central composite design (4 factors, 5 levels), and modeling of response surfaces.	Applied for quality control method	(Rocha and Lourenço, 2023)
14.	Dilitiazem, Propranolol+HCTZ	Mixed-mode RP-HPLC (Analytical QbD)	Mixed-mode stationary phase. Separation achieved in more than 8min under isocratic elution. Method development followed Analytical Quality by Design (QbD) principle with risk assessment 2- level fractional factorial screening and central composite design optimization. Method operable design established using Monte Carlo simulation and capability analysis.	Applied to *in vitro* release sample from 3D printed tablet	(Samara *et al*., 2024)

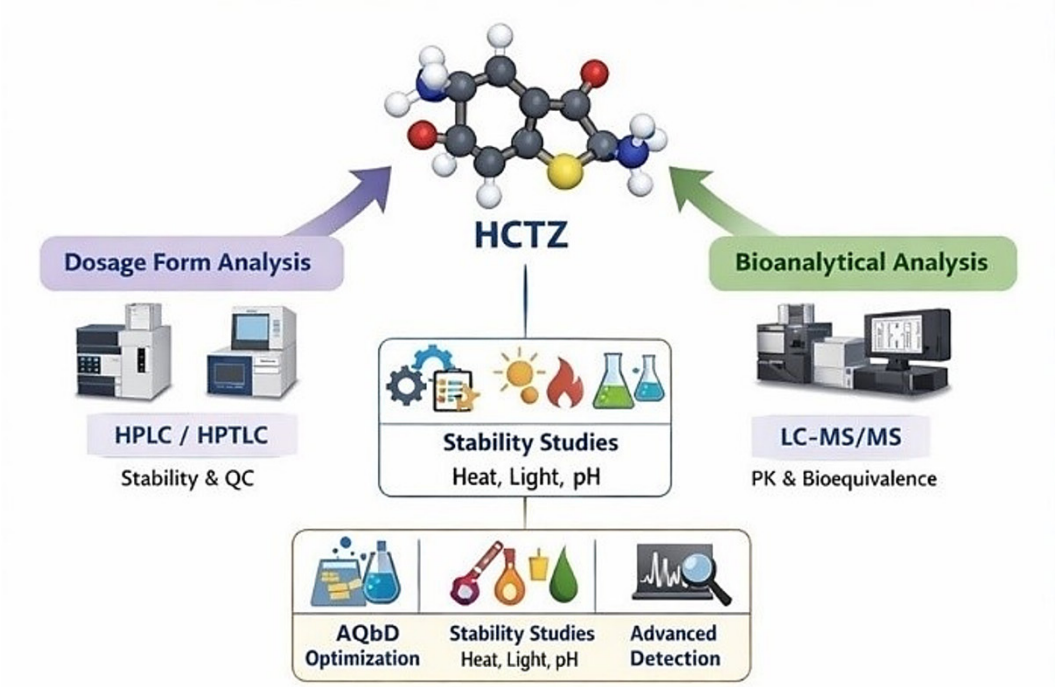

Figure 1: Conceptual framework of analytical approaches for HCTZ in fixed-dose combinations.

Research Gaps

In conclusion, the studied methodologies provide a solid analytical framework for quality assurance, regulatory evaluation of HCTZ containing fixed dose combinations. Nonetheless, the available literature suggests a research deficit in the development of AQbD-oriented, stability indicating and environmentally sustainable analytical methods capable of estimating HCTZ in combination with routinely co-formulated antihypertensive drugs. In particular, there has been little attention on systematic method optimization using design space concepts and validation of technique suitable for routine quality control.

CONCLUSION

This study focuses on the analytical methodologies developed for simultaneous quantification of HCTZ with diverse antihypertensive drugs in pharmaceutical formulations and biological matrices. Conventional HPLC and HPTC producer remain important in routine quality control because to their simplicity, accuracy, and cost effectiveness. Meanwhile, LC-MS/MS technologies have become indispensable in bioanalytical applications, providing the sensitivity and selectivity required for pharmacokinetics, bioequivalence and interaction studies. The growing use of stability -indicating methods and AQbD-driven analytical development fits recent regulatory demands while ensuring method robustness across the product lifecycle. Furthermore, the application of this analytical approach to modern drug delivery system, such as fixed - dose combination drugs and 3D- printed tablets, illustrates their adaptability and future utility.

To summarise, the reviewed approaches provided a solid analytical platform for the quality assurance, regulatory evaluation, and clinical investigation of HCTZ - containing combined dosage forms. The further integration of AQbD principles and advanced detections techniques is anticipated to improve analytical performance and support changing landscape of pharmaceutical research.

ACKNOWLEDGEMENT

The authors gratefully acknowledge SBV University Puducherry and East West College of Pharmacy Bangalore for providing guidance and support for this review work.

ABBREVIATIONS

HCTZ: Hydrochlorothiazide; **ACE:** Angiotensin-Converting Enzyme; **AQbD:** Analytical Quality by Design; **UV:** Ultraviolet-Visible; **LC-MS/MS:** Liquid Chromatography-Tandem Mass Spectrometry; **RP-HPLC:** Reverse Phase High Performance Liquid Chromatography; **HPTLC:** High Performance Thin Layer Chromatography; **ARBs:** Angiotensin Receptor Blockers; **CDSCO:** Central Drug Standard Control Organization; **MRM:** Multiple Reaction Monitoring; **ESI:** Electrospray Ionization; **LLE:** Liquid-Liquid Extraction; **SPE:** Solid Phase Extraction; **DoE:** Design of Experiments; **ATP:** Analytical Target Profile; **BDS:** Base Deactivated Silica; **ODS:** Octadecylsilane.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

V Sree Janardhanan: conceptualization, supervision, editing and final approval of the manuscript. **Nandini Goudar:** Literature survey, data collection, analysis and interpretation, manuscript drafting, preparation of tables and referencing. Both authors contributed to manuscript revision and approved the final version of publication.

REFERENCES

Al-Asmar, A., Kittana, N., Mayyala, A., Asmar, I., and Hussein, A. (2025). Development and Validation of an UPLC-MS/MS Method for Simultaneous Quantification of Bisoprolol and Hydrochlorothiazide in Human Plasma. *Journal of Mass Spectrometry*, *60*(8), e5159. https://doi.org/10.1002/jms.5159

Bakshi, M., and Singh, S. (2002). Development of validated stability-indicating assay methods—Critical review. *Journal of Pharmaceutical and Biomedical Analysis*, *28*(6), 1011-1040. https://doi.org/10.1016/S0731-7085(02)00047-X

Bharathi, D. V., Hotha, K. K., Chatki, P. K., Satyanarayana, V., and Venkateswarlu, V. (2012). Lc-MS/MS Method For Simultaneous Estimation of Candesartan And Hydrochlorothiazide in Human Plasma And Its Use in Clinical Pharmacokinetics. *Bioanalysis*, *4*(10), 1195-1204. https://doi.org/10.4155/bio.12.83

Blessy, M., Patel, R. D., Prajapati, P. N., and Agrawal, Y. K. (2014). Development of forced degradation and stability indicating studies of drugs-A review. *Journal of Pharmaceutical Analysis*, *4*(3), 159-165. https://doi.org/10.1016/j.jpha.2013.09.003

Central Drugs Standard Control Organization.. List of FDC and subsequent new drugs approved in India. Retrieved August 29, 2025, from https://cdsco.gov.in/opencms/opencms/en/Approval_new/FDC-New-Drugs-Marketing/

Ganna, A., Vaithiyanathan, S. J., V P, P., and P, V. (2022). Multiresponse Optimization of HPLC Method: Simultaneous Estimation of Protease Inhibitors and NNRTI in Human Plasma. *Journal of Chromatographic Science*, *60*(3), 224-231. https://doi.org/10.1093/chromsci/bmab067

Gaurkhede, R. M., and Chandewar, A. V. (2018). Analytical Method Development and Validation for Simultaneous Estimation of Candesartan Cilexetil and Hydrochlorothiazide in Tablet Dosage form. *Research Journal of Pharmacy and Technology*, *11*(2), 459. https://doi.org/10.5958/0974-360X.2018.00084.7

Gradman, A. H. (2010). Rationale for Triple-Combination Therapy for Management of High Blood Pressure. *The Journal of Clinical Hypertension*, *12*(11), 869-878. https://doi.org/10.1111/j.1751-7176.2010.00360.x

Herman, L. L., Padala, S. A., and Ahmed, I. (2023). Hydrochlorothiazide. In StatPearls. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK470386/

Jeon, S.-Y., Jeon, J.-H., Park, J.-H., Lee, J., Pang, M., Choi, M.-K., and Song, I.-S. (2022). Simultaneous Analysis of a Combination of Anti-Hypertensive Drugs, Fimasartan, Amlodipine, and Hydrochlorothiazide, in Rats Using LC-MS/MS and Subsequent Application to Pharmacokinetic Drug Interaction with Red Ginseng Extract. *Toxics*, *10*(10), 576. https://doi.org/10.3390/toxics10100576

Karvelis, D., Kalogria, E., and Panderi, I. (2014). A Stability-Indicating HPLC Method for the Quantification of Aliskiren and Hydrochlorothiazide in a Pharmaceutical Formulation. *Journal of AOAC INTERNATIONAL*, *97*(6), 1519-1525. https://doi.org/10.5740/jaoacint.13-383

Liu, F., Xu, Y., Gao, S., Zhang, J., and Guo, Q. (2007). Determination of hydrochlorothiazide in human plasma by liquid chromatography/tandem mass spectrometry. *Journal of Pharmaceutical and Biomedical Analysis*, *44*(5), 1187-1191. https://doi.org/10.1016/j.jpba.2007.04.020

Ma, L., Zheng, K., Yan, J., and Cheng, W. (2021). Efficacy of ARB/HCTZ Combination Therapy in Uncontrolled Hypertensive Patients Compared with ARB Monotherapy: A Meta-Analysis. *International Journal of Hypertension*, *2021*, 1-7. https://doi.org/10.1155/2021/6670183

MacDonald, T. M., Williams, B., Webb, D. J., Morant, S., Caulfield, M., Cruickshank, J. K., Ford, I., Sever, P., Mackenzie, I. S., Padmanabhan, S., McCann, G. P., Salsbury, J., McInnes, G., Brown, M. J., and for The British Hypertension Society Programme of Prevention And Treatment of Hypertension With Algorithm-based Therapy (PATHWAY). (2017). Combination Therapy Is Superior to Sequential Monotherapy for the Initial Treatment of Hypertension: A Double-Blind Randomized Controlled Trial. *Journal of the American Heart Association*, *6*(11), e006986. https://doi.org/10.1161/JAHA.117.006986

Palakurthi, A. K., Dongala, T., and Katakam, L. N. R. (2020). QbD based development of HPLC method for simultaneous quantification of Telmisartan and Hydrochlorothiazide impurities in tablets dosage form. *Practical Laboratory Medicine*, *21*, e00169. https://doi.org/10.1016/j.plabm.2020.e00169

Patel, J. R., Pethani, T. M., Vachhani, A. N., Sheth, N. R., and Dudhrejiya, A. V. (2014). Development and validation of bioanalytical method for simultaneous estimation of ramipril and hydrochlorothiazide in human plasma using liquid chromatography-tandem mass spectrometry. *Journal of Chromatography B*, *970*, 53-59. https://doi.org/10.1016/j.jchromb.2014.08.023

Rane, V. P., Patil, K. R., Sangshetti, J. N., Yeole, R. D., and Shinde, D. B. (2010). Stability Indicating LC Method for Simultaneous Determination of Irbesartan and Hydrochlorothiazide in Pharmaceutical Preparations. *Journal of Chromatographic Science*, *48*(7), 595-600. https://doi.org/10.1093/chromsci/48.7.595

Rane, V. P., Sangshetti, J. N., and Shinde, D. B. (2008). Simultaneous High-Performance Liquid Chromatographic Determination of Telmisartan and Hydrochlorothiazide in Pharmaceutical Preparation. *Journal of Chromatographic Science*, *46*(10), 887-891. https://doi.org/10.1093/chromsci/46.10.887

Rocha, A. L., and Lourenço, F. R. (2023). Development and optimization of a LC-MS/MS compatible method for quantification of losartan, hydrochlorothiazide and their impurities using AQbD approach and measurement uncertainty evaluation. *Talanta*, *259*, 124481. https://doi.org/10.1016/j.talanta.2023.124481

Salvadori, M. C., Moreira, R. F., Borges, B. C., Andraus, M. H., Azevedo, C. P., Moreno, R. A., and Borges, N. C. (2009). Simultaneous Determination of Losartan and Hydrochlorothiazide in Human Plasma by LC/MS/MS with Electrospray Ionization and Its Application to Pharmacokinetics. *Clinical and Experimental Hypertension*, *31*(5), 415-427. https://doi.org/10.1080/10641960802668714

Samara, I. M., Ntorkou, M., Gioumouxouzis, C. I., Karavasili, C., Tzanavaras, P. D., and Zacharis, C. K. (2024). Analytical QbD for the optimization of a multimode HPLC method for the investigation of hydrochlorothiazide, diltiazem and propranolol release from 3D printed formulation. *Journal of Pharmaceutical and Biomedical Analysis*, *248*, 116324. https://doi.org/10.1016/j.jpba.2024.116324

Shah, J. V., Parekh, J. M., Shah, P. A., Shah, P. V., Sanyal, M., and Shrivastav, P. S. (2017). Application of an LC-MS/MS method for the analysis of amlodipine, valsartan and hydrochlorothiazide in polypill for a bioequivalence study. *Journal of Pharmaceutical Analysis*, *7*(5), 309-316. https://doi.org/10.1016/j.jpha.2017.06.001

Shah, N., Suhagia, B., Shah, R., and Patel, N. (2009). HPTLC method for the simultaneous estimation of valsartan and hydrochlorothiazide in tablet dosage form. *Indian Journal of Pharmaceutical Sciences*, *71*(1), 72. https://doi.org/10.4103/0250-474X.51967

Volpe, M. and Tocci. (2012). Rationale for triple fixed-dose combination therapy with an angiotensin II receptor blocker, a calcium channel blocker, and a thiazide diuretic. *Vascular Health and Risk Management*, 371. https://doi.org/10.2147/VHRM.S28359

Cite this article: Vaithiyanathan SJ, Goudar N. Emerging Analytical Strategies for Screening Hydrochlorothiazide in Fixed Dose Combinations - A Comprehensive Review. Int. J. Pharm. Investigation. 2026;16(4):1377-83.