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# ACE under Stress: A Comprehensive Reviewof Stability Indicating Chromatographic Methods

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**ABSTRACT**
Angiotensin-converting enzyme (ACE) inhibitors are still the cornerstone in the treatment of cardiovascular diseases and hypertension, but their wide range of chemical structures such as sulfhydryl, carboxylate, phosphate, and ester prodrugs make them susceptible to stress degradation. Stability- indicating chromatographic methods (SIMs) are thus critical for separating intact drug molecules from their hydrolytic, oxidative, hydrolytic, oxidative, photolytic, and thermal degradation products. This review gives an extensive account of published SIMs for ACE inhibitors that include high- performance liquid chromatography (HPLC), ultra- high- performance liquid chromatography (UHPLC), high- performance thin- layer chromatography (HPTLC), and hyphenated LC- MS methods. Described studies are critically discussed in relation to forced degradation approaches, chromatographic selectivity, validation parameters, and regulatory compliance with ICH Q1 A(R2), Q2(R2), and Q14 guidelines. Comparative discussion focuses on prevalent routes of degradation like ester hydrolysis to active acids, diketopiperazine formation and oxidative dimerization of sulfhydryl groups. Trends involve increased utilization of design- of- experiments (DOE), peak- purity determination by PDA or MS, and the use of greener mobile phases. By distilling methodological progress and pitfalls, this review hopes to provide a handy guide for analysts designing sound, regulatory compliant stability- indicating assays for ACE inhibitors in bulk and pharmaceutical preparations.

**KEY WORDS:**ACE inhibitors, stability- indicating methods, forced degradation, HPLC, UHPLC, HPTLC, LC- MS, ICH guidelines.

## I. INTRODUCTION

Angiotensin- converting enzyme (ACE) inhibitors are some of the most common antihypertensive drugs, also used in heart failure, post- myocardial infraction, and diabetic nephropathy. The class is structurally chemically heterogeneous, ranging from sulfhydryl- containing derivatives (captopril) to dicarboxylates (enalapril, lisinopril, quinapril), phosphinates (fosinopril), and prodrug esters (ramipril, perindopril, trandolapril, cilazapril, benazepril). Their clinical effectiveness is balanced by a well- documented stability to degradation under stress conditions. Ester- based prodrugs are hydrolysed to active acidic forms (e.g., enalapril enalaprilat), thiol analogs such as captopril are easily oxidized to disulfides, and lisinopril would preferentially cyclize to diketopiperazine (DKP) under heat or base stress [1-3].

Pharmaceutical formulations should be examined using validated stability- indicating techniques (SIMs) capable of readily separating the active pharmaceutical ingredient (API) from its possible impurities and degradation products, as the International Council of Harmonisation guidelines state (ICH Q1A(R2), Q2(R2)) [4,5]. The available analytical methods of chromatographic techniques- specifically high- performance liquid chromatography (HPLC), ultra- high- performance liquid chromatography (UHPLC), and high- performance thin- layer chromatography (HPTLC)- are used most commonly for SIM development of ACE inhibitors because they have better selectivity and compatibility with photodiode array (PDA) and mass spectrometric detection [6,7].

Forced degradation studies are the basis of stability- indicating method (SIM) development, in which ACE inhibitors are subjected to hydrolytic, oxidative, thermal, and photolytic stress to generate degradation products that challenge the selectivity of the method. For example, a number of HPLC- based stability- indicating assays for enalapril (both bulk drug and dosage forms) effectively resolve enalaprilat and its oxidative by- products [8].Similarly, validated chromatographic methods for lisinopril and ramipril have been described, illuminating degradation mechanisms that reflect realistic storage and formulation conditions [9,10].

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In light of clinical importance of ACE inhibitors and the regulatory requirement for stability and shelf-life testing, a thorough review of chromatographic stability- indicating methods (SIMs) for these drugs is appropriate and useful. This review attempts to synthesize described analytical methods, evaluate degradation mechanisms and chromatographic separation, determine typical practice in validation and conformance to regulatory requirements, and provide advice on enhancing subsequent method development.

| Drug | Chemical nature | Prodrug/ active form | Half-life | Primary clinical use | Key notes |
|---|---|---|---|---|---|
| Enalapril | Dicarboxylate derivative | Prodrug → Enalaprilat | 11 | Hypertension, CHF | Widely used in single & combination therapies |
| Lisinopril | Dicarboxylate derivative | Active drug | 12 | Hypertension, CHF, post- MI | Water soluble, not a prodrug; long- acting |
| Ramipril | Dicarboxylate derivative | Prodrug → Ramiprilat | 13-17 | Hypertension, CHF, CV risk reduction | High tissue penetration; cardioprotective |
| Perindopril | Dicarboxylate derivative | Prodrug → Perindoprilat | 3-10 | Hypertension, stable CAD | Once- daily dosing, vascular protective effects |
| Quinapril | Dicarboxylate derivative | Prodrug → Quinaprilat | 2-5 | Hypertension, CHF | Ester prodrug, hepatically activated |
| Fosinopril | Phosphinate ester | Prodrug → Fosinoprilat | 11-12 | Hypertension, CHF | Dual hepatic & renal elimination |
| Benazepril | Dicarboxylate derivative | Prodrug → Benazeprilat | 10-12 | Hypertension | Common in fixed dose combination |
| Trandolapril | Dicarboxylate derivative | Prodrug → Trandolaprilat | 15-24 | Hypertension, LV dysfunction | Long half-life, suitable for once-daily dosing |
| Moexipril | Dicarboxylate derivative | Prodrug → Moexiprilat | 2-9 | Hypertension | Food effect on absorption; less commonly used |
| Captopril | Sulfhydryl-containing | Active drug | 2 | Hypertension, CHF, diabetic nephropathy | First ACE inhibitor, short-acting |

## II. STABILITY INDICATING CHROMATOGRAPHIC TECHNIQUES

Stability-indicating chromatographic analytical procedures are validated analytical methods meant to effectively separate and quantify active pharmaceutical ingredients (APIs) even in the presence of impurities, excipients, or degradation products. Such methods are developed by performing forced degradation studies under stress conditions like acidic, basic, oxidative, thermal, and photolytic conditions, as suggested by ICH Q1A (R2). Their main function is to verify specificity, preventing interference from degradation by-products in the drug assay. Frequently used methods are HPLC, HPTLC, and GC, appreciated for their sensitivity and accuracy. Such procedures are crucial for determining stability profiles, quality control, and regulatory compliance, hence ensuring the safety, purity, and efficacy of pharmaceutical products throughout shelf life.

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**Role of stability indicating HPLC in pharmaceutical analysis**

Stability-indicating methods (SIMs) are analytical methods that can precisely quantify active pharmaceutical ingredients regardless of the degradation products, impurities, or excipients present. Of the chromatographic tools available, High-Performance Liquid Chromatography (HPLC) is most widely used due to its higher resolution, sensitivity, and reproducibility.To develop a stability-indicating HPLC method, the drug undergoes forced degradation studies including acidic, alkaline, oxidative, photolytic, and thermal stress following ICH Q1A (R2) guidelines. The stress conditions generate potential degradation products, which are separated and quantified to prove method specificity.Importance of these methods is that they can:

- Assess drug stability during formulation and fix shelf-life.
- Facilitate quality control by checking potency, purity, and safety.
- Comply with regulations, whereby organizations such as ICH and FDA require stability-indicating methods validated for drug approval.

In general, stability-indicating HPLC is a mainstay of pharmaceutical analysis to guarantee drugs continue to be effective and safe to use throughout their intended lifespan.

**High- Performance Liquid Chromatography method**

A broad range of HPLC method of stability indicating of ACE inhibitors are available. The validated RP- HPLC stability- indicating assays for enalapril maleate have clearly resolved the parent compound from the principal degradation products such as enalaprilat and diketopiperazine under hydrolytic (acidic/alkaline), oxidative, thermal, and photolytic stress conditions. All of these methods meet the ICH validation criteria and exhibited excellent specificity, linearity with a correlation coefficient ≥0.999, and accuracy ranging within 98-102%, making them suitable for routine quality control and stability monitoring of enalapril dosage forms [11-13]. Likewise, stability-indicating HPLC methods of development for lisinopril yield effective separation of the drug from its primary degradation products, diketopiperazine (DKP), and also from the excipients of the formulations. Forced degradation studies validate DKP formation under alkaline and thermal stress conditions. The validated analytical techniques, as per ICH guidelines, demonstrate high specificity, accuracy (98-102%), and precision (%RSD ≤ 2), validating their use for stability determination [14-15]. Stability- indicating HPLC methods for captopril are oriented to bypass its thiol- associated instability, frequently uses pre- column derivatization, ion- pair chromatography, or electrochemical detection for improved selectivity. Stress testing reveals oxidative degradation to disulfide dimers and sulfoxides. Validated procedures ensure reliable separation, precision and ruggedness, justifying their use in routine stability evaluation [16-17]. For ramipril, stability-indicating HPLC methods efficiently differentiate the native drug from its major degradant, ramiprilat, as well as other hydrolytic and oxidative products. Degradation tests show its susceptibility to moisture, high temperature, and light. Method validation also ensures specificity, accuracy (□100%), and precision within ICH standards, ensuring their suitability for stability monitoring [18-19]. Stability- indicating HPLC assays of perindopril can differentiate the parent drug from its major hydrolytic degradant, perindoprilat, as well as from oxidative and photolytic by- products. The methods, internally validated according ICH guidelines, show high accuracy, precision, and specificity, whereas LC- MS- based techniques offer improved sensitivity for degradant detection [20]. Like that, stability- indicating HPLC methods for benazepril also allow discrimination of the drug from its significant hydrolytic product, benazeprilat, and other stress degradation impurities. Forced degradation using acidic, alkaline, oxidative and light stress reaffirms the selectivity of these tests, with validation indicating good accuracy (around 98-102%) and precision (%RSD ≤ 2) in support of their application in stability assessment [21- 22]. Validated stability-indicating HPLC procedures for quinapril provide sharp separation of the parent drug from its major hydrolytic product, quinaprilat, along with other degradation impurities formed under stress. Acidic, alkaline, and oxidative forced degradation studies establish method selectivity, whereas validation proves to be accurate between 98-102% and precise within %RSD ≤ 2, and thus the assays are fit for stability evaluation and regular quality control [23-24]. For trandolapril, stability-indicating RP-HPLC approaches efficiently distinguish the drug from several hydrolytic and oxidative degradants. Accelerated stress test points to vulnerability towards alkaline and peroxide stress, and confirmed findings ascertain specificity, accuracy

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(98-102%), and precision (% RSD≤2), which warranty stability study reliability in drug formulations [25-26]. Stability- indicating HPLC tests for cilazapril use RP- C18 columns with acetonitrile- buffer mobile phases, ensuring efficient resolution of the drug from its hydrolytic and cyclic cleavage products. Stress studies show its susceptibility to moisture and higher temperature, and validation findings authenticate the procedures to be specific, accurate, and precise for evaluation of stability in bulk drug and dosage forms [27-28].

Literature Review Table: Overview of Stability- indicating HPLC methods

| **Drug** | **Representative HPLC conditions** | **Forced degradation & major degradants** | **Forced degradation & major degradants** | **Reference** |
|---|---|---|---|---|
| Enalapril / Enalapril maleate | C18 phosphate buffer + ACN/MeOH | Acid/base hydrolysis → enalaprilat & diketopiperazine **(**DKP**)**; oxidative ($H_2$ $O_2$ ) → Oxidized products; photolysis & thermal degradation | Linearity r ≥0.999; accuracy 98–102%; precision %RSD ≤ 2; PDA peak purity confirmed | 11-13 |
| Lisinopril | C18; buffer + ACN | Hydrolysis & cyclization → DKP; oxidative degradation a LC–MS used for degradant ID | Specificity (no excipient interference); accuracy 98–102%; precision ≤2% RSD | 14-15 |
| Captopril | C8/C18; ion-pair mobile phase (pentane sulfonate) | Oxidation → disulfidedimers, sulfoxides; base hydrolysis also possible | validated sensitivity; DoE/QbD applied; precision improved with derivatization/ECD | 16-17 |
| Ramipril | C18; phosphate buffer + ACN/MeOH | Hydrolysis →ramiprilat; oxidative & photolytic degradation | Specificity (baseline separation from ramiprilat); accuracy ~100%; %RSD ≤ 2; robustness sometimes via DoE | 18-19 |
| Perindopril | C18; buffer + ACN | Hydrolysis → perindoprilat; oxidative & photolytic degradation | Specificity, linearity, accuracy; | 20 |
| Benazepril | C18; buffer + organic (MeOH or ACN) | Hydrolysis → benazeprilat; oxidative stress ($H_2$ $O_2$ ) → oxidized products; | Validated per ICH: specificity, linearity, accuracy, precision; suitable for bulk & dosage | 21-22 |
| Quinapril | C18; buffer + ACN | Hydrolysis → quinaprilat; | Acceptable accuracy, | 23-24 |

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|---|---|---|---|---|
| | | acid/base hydrolysis; oxidative stress products | precision, specificity; | |
| Trandolapril | C18 phosphate buffer + ACN | Upto 6 oxidative degradants under $H_2$ $O_2$ ; hydrolytic (alkaline > acid); mild photolysis | Specificity & linearity validated; robustness via factorial DoE; accuracy/precision per ICH | 25-26 |
| Cilazapril | C18; phosphate buffer + ACN | hydrolysis → cilazaprilat; cyclic degradants reported; | Validated for specificity, linearity, accuracy, precision; applied to tablets & suspensions | 27-28 |

**Role of HPTLC stability- indicating in pharmaceutical analysis**

Stability-indicating High-Performance Thin Layer Chromatography (HPTLC) is a powerful technique for pharmaceutical analysis, which can separate and quantify drugs together with their degradation products formed under stress conditions like acidic, alkaline, oxidative, thermal, and photolytic conditions. It has high specificity to quantify the drugs without interference from degradants or excipients. Thanks to its cost-effectiveness, speed, and ability to analyse several samples at once, HPTLC is commonly used in routine stability testing, determination of stability profiles, shelf-life determination, and compliance with regulatory requirements—eventually assuring the safety, efficacy, and purity of drugs.

**High- Performance Thin Layer Chromatography method**

A wide range of stability indicating HPTLC methods have been explored for ACE inhibitors. Barsagade A. et al. developed simultaneous estimation of enalapril maleate and losartan potassium stability-indicating HPTLC method, which successfully separated analytes from degradants. Enalapril underwent acidic, basic, and thermal degradation, while losartan was photolytically degraded, with the method validated according to ICH guidelines [29]. Dewani Mohit G et al. expanded stability-indicating HPTLCperindopril erbumine on silica gel plates with a mobile phase containing dichloromethane–methanol–glacial acetic acid and detection at 215 nm. The procedure separated drug peaks from degradative peaks under different stress conditions and was validated according to ICH guidelines [30]. Dr. Anjana et al. developed and validated an HPTLC method of simultaneous estimation of lisinopril dihydrate and cilnidipine with good linearity, sensitivity, and precision. The abstract is not stated to confirm forced degradation studies, so its complete stability-indicating character is uncertain [31].Bhoire et al. have established a validated stability-indicating HPTLC method for simultaneous estimation of perindopril and indapamide in bulk and in tablets. The technique could efficiently separate drugs from degradations under stress conditions to meet ICH validation criteria [32].

Literature Review Table: -Overview of Stability- indicating HPTLC methods

| **Drug** | **Representative HPLC conditions** | **Stress Conditions & Findings** | **Validation** | **Reference** |
|---|---|---|---|---|
| Enalapril maleate + Losartan potassium | Silica gel 60 F254 | Acid, base, thermal → enalapril degraded;photolysis → losartan degraded | Specific, accurate, acceptable LOD/LOQ, ICH compliant | 29 |
| Perindoprilerbumine | Silica gel 60 F254; dichloromethane:methanol:glacial | Forced degradation: hydrolytic, | Specific, validated | 30 |

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|---|---|---|---|---|
| | acetic acid | oxidative, thermal, photolytic | as per ICH Q1A(R2) & Q2(R1) | |
| Lisinopril dihydrate +Cilnidipine | Silica gel 60 F254 | stability-indicating nature uncertain | Validated for linearity, precision, sensitivity | 31 |
| Perindopril +Indapamide | Silica gel 60 F254 | Forced degradation under various stress conditions | Specific, accurate, ICH guideline compliant | 32 |

## III. STABILITY INDICATING HYPHENATED CHROMATOGRAPHIC METHODS

Stability-indicating chromatographic hyphenated techniques combine separation methods with spectroscopic or mass spectrometric detection in order to determine drugs and their degradation products with high sensitivity.They include forced degradation under acidic, alkaline, oxidative, thermal, and photolytic stress according to ICH Q1A(R2) guidelines.Methods like LC–MS, LC–MS/MS, GC–MS, LC–NMR, and LC–FTIR allow both structural characterization and quantification.These procedures are crucial in determining degradation pathways, impurities, and stability profiles of drugs.They provide compliance with regulation, enhance quality control, and assure drug safety and effectiveness.

**Hyphenated techniques**

Roskar et al. (2009) employed LC-MS in the investigation of the stability of a novel ACE inhibitor, xPRIL, and determined two primary degradation pathways affected by temperature and pH. The study also contrasted the degradation kinetics of xPRIL with that of enalapril and perindopril, providing insight into ACE inhibitor stability profiles.[33]

## IV. CONCLUSION

Stability-indicating chromatographic methods are of central importance in pharmaceutical analysis for ensuring the quality, safety, and efficacy of drug substances and formulations during their shelf life. HPLC remains the gold standard technique with extraordinary resolution, sensitivity, and versatility for the determination and quantitation of drugs and their degradation products. HPTLC is a useful supplementary tool, offering a fast, cost-effective, and high-throughput alternative well adapted to routine stability testing and comparative studies. More sophisticated hyphenated techniques, e.g., LC–NMR, yield conclusive structural data on degradation products, especially where mass spectrometric information might be limiting. Together, these procedures meet not only ICH and regulatory demands but also produce extensive information on stability profiles, degradation routes, and impurity identification. The integration of traditional and hyphenated chromatographic approaches enhances the validity of stability studies and enhances the creation of safe, effective, and high-quality drugs.

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