REVIEW ARTICLE

Analytical Strategies for Stability-Indicating Method Development: Challenges and Advances in Fixed-Dose Combination Formulations

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ABSTRACT

Stability-indicating methods (SIMs) in the pharmaceutical industry are critical to guaranteeing product safety, efficacy, and compliance with regulatory requirements, especially for fixed-dose combination (FDC) formulations. The review addresses both advancements and challenges in SIMs by confronting the tremendous complexities posed by the presence of multiple active pharmaceutical ingredients (API) and their degradation pathways. The review surveys some works in which degradation products were investigated using traditional and novel methods, from HPLC, UHPLC, and HPTLC to spectroscopic techniques, on to the hyphenated techniques of LC-MS and GC-MS. The concepts of forced degradation and regulatory input found great emphasis along with advances such as AI-driven optimization, green chemistry, and real-time stability monitoring. Directions for future studies focus on implementing automation, environmentally-friendly methods, and hybrid techniques in a way that maximizes efficiency and viability and aligns with a rapidly changing regulatory environment. Therefore, this review underlines the need for robust, specific, and cost-effective SIMs to guarantee the long-term stability of FDC formulations.

Keywords: Stability-indicating methods, fixed-dose combination, forced degradation, analytical techniques, HPLC, UHPLC, hyphenated techniques

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INTRODUCTION

Fixed-dose combinations, or FDCs, are a part of pharmaceutical research that is increasingly being studied with regard to patients' compliance, reduced pill burden, and increas-ing therapeutic efficacy.[1] FDCs exert any additive or synergistic therapeutic efficacy by virtue of having two or more active pharmaceutical ingredients (APIs) in one dosage form, particularly for the treatment of very specific chronic diseases, which includes hypertension, diabetes, and certain infectious diseases, among others.[2] On the other hand, these features of FDCs pose serious challenges in performing analytical testing-related studies, especially concerning their stability studies.[3] Monitoring the stability of each API, along with degradation products and anything else that could interfere, greatly calls for highly selective and robust analytical methods development.[4]

Stability-indicating methods (SIMs) are generally recognized as major analytical tools for pharmaceutical applications, which capitalize on the differences in reaction profiles of the APIs to be examined and their degradation products when subjected to stress conditions.[5] These methodologies also apply a cut-off value for the degradation impurities with a retroactive assurance that they pose no safety, efficacy, or quality of the drug in question.[6] The main aim of SIMs is to ensure the analysis of intact drug substances and any possible degradation products with no interference from excipients, impurities, or the formulation matrix. The technical and regulatory hurdles that this poses are very complex for SIMs, owing to the nature of FDCs under study.[7]

Drug safety and efficacy have become assured by the regulatory authorities around the world through extensive guidelines for drug development and the associated validation of SIMs.[8] The International Council for Harmonisation (ICH) Q3B guidelines direct recommendations toward identifying degradation products and qualifying them during the development of new drug formulations.[9] ICH Q2(R1) has set up the criteria for validation of analytical procedures in relation to stability testing and, in these contexts, specific parameters such as specificity, accuracy, precision, linearity, and robustness are required to be fulfilled.[10] For chromatographic techniques, the United States Pharmacopeia (USP) prescribes an upper limit of recommendations to ensure robustness and system suitability in pharmaceutical analysis.[11] Essentially, anything that demonstrates that the method is compliant will also show evidence for regulators (FDA, EMA, and any other global bodies) to be satisfied.

The formulation of SIMs for FDCs remains difficult despite the provisions of the regulatory framework. With a multitude of APIs having dissimilar physical and chemical properties and therefore a great possibility of degradation

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Table 1: The chromatography techniques used for stability-indicating method (SIM) development

Chromatographic Technique	Primary Use	Resolution	Sensitivity	Detection Enhancement
High-Performance Liquid Chromatography (HPLC)	Stability testing of pharmaceuticals	Excellent	High	UV-Vis, Fluorescence, Mass Spectrometry (MS)[19]
Ultra-High-Performance Liquid Chromatography (UHPLC)	Detection of low-level degradation products in FDCs	Higher than HPLC	Improved	UV-Vis, Mass Spectrometry (MS)[20]
Gas Chromatography (GC)	Detection of volatile compounds	Good	Moderate	Flame Ionization Detection (FID), GC-MS[21]
Thin-Layer Chromatography (TLC)	Preliminary stability screening	Moderate	Low	Visual, Densitometry[22]

pathways, the analytical techniques for stability testing should be excellent and peaked with multiple capabilities.[12]. Interactions of API with excipients further complicate degradation profiles and thus pose additional challenges to method development. Solving such challenges would require a multidisciplinary approach involving modern analytical technologies and an in-depth understanding of degradation chemistry.[13]

The analytical methods used for arriving at the stability-indicating methods for FDC formulation shall be discussed in detail in this review. The review intends to provide insight into the newest developments in chromatography, spectroscopy, and emerging analytical techniques and their application in stability-studying. The challenges in the development parameters of the methods will also be told, including drug-drug interaction, interference from excipients, and regulations. Moreover, two case studies will be discussed, including green analysis and AI-based method optimization, shedding light on the changing dynamics of pharmaceutical stability testing. Finally, the current review will end with perspectives on future trends for developing stability-indicating methods, especially focusing on automation, AI, and new analytical tools to tend to make stability studies for FDCs more efficient and trustworthy.

Concept of Stability-Indicating Methods

Definition and Purpose of Stability-Indicating Methods (SIMs)

A Stability-Indicating Method (SIM) is an analytical method proved to establish the detection, quantification, and separation of the active pharmaceutical ingredients (APIs) from their degradation products, impurities, and excipients in a drug formulation. The primary objective of an SIM is to provide a comprehensive picture of any chemical or physical changes that have occurred in the drug over time regarding their identification and quantification to ascertain the stability, efficacy, and safety of the drug. Unlike general analytical methods that merely quantify the API content, SIMs are developed for giving an evaluation of the stability of the entire formulation under various stress conditions, such as heat, humidity, light, and oxidation.[14]

The International Council for Harmonisation (ICH) Q1A (R2) task force guidelines mention that stability studies are vital for establishing shelf life and storage conditions for pharmaceutical products. This provides Herculean insight into any degradation pathways, thereby aiding formulators and regulatory agencies in rating the risk of stability-related failures. The stability of each API in a fixed-dose combination (FDC) may add different challenges to the structure; therefore, developing an SIM for such formulations presents unique challenges requiring highly selective analytical techniques.[15]

Role of SIMs in Quality Control within the Pharmaceutical Industry

The pharmaceutical industry is tightly regulated to secure the safety and efficacy of drug products during their valid duration. This brings stability-indicating methods into the primary focus of pharmaceutical quality control (QC) in the sense that:

Detection of Degradation Products

SIM detects and quantifies degradation products formed through various chemical or physical mechanisms that may be the consequence of the instability of the drug

Table 2: The spectroscopic methods used in stability-indicating method (SIM) development

Spectroscopic Technique	Primary Use	Structural Information Provided	Detection Sensitivity	Common Combinations
Ultraviolet-Visible (UV-Vis) Spectroscopy	Detecting and quantifying degradation products	Absorbance properties of degradation products	High	Often combined with HPLC[23]
Infrared (IR) Spectroscopy (FTIR)	Identifying functional groups in degradation pathways	Functional group identification	Moderate	Can be coupled with chromatography[24]
Nuclear Magnetic Resonance (NMR) Spectroscopy	Elucidating complex degradation mechanisms	Detailed structural insights into degradation products	High	Can be used standalone or with chromatography[25]
Mass Spectrometry (MS)	Determining molecular weight and fragmentation patterns	Molecular weight and fragmentation patterns	Very High	Often combined with HPLC or GC[26]

Table 3: The hyphenated techniques used in stability-indicating method (SIM) development

Hyphenated Technique	Primary Use	Advantages	Detection Sensitivity	Common Applications
HPLC-MS/MS (Liquid Chromatography-Mass Spectrometry)	Detection of low-level degradation products	High sensitivity and specificity in degradation product detection	Very High	Pharmaceutical stability, impurity profiling[27]
GC-MS (Gas Chromatography-Mass Spectrometry)	Analyzing volatile degradation products	Ideal for volatile compounds, improved identification of unknowns	High	Volatile compound analysis, thermal degradation[28]
LC-NMR (Liquid Chromatography-Nuclear Magnetic Resonance)	Separation and structural elucidation of degradation products	Provides both separation and detailed structural insights	High	Degradation pathway elucidation, structural characterization[29]
CE-MS (Capillary Electrophoresis-Mass Spectrometry)	Analysis of highly polar and charged compounds	High resolution for polar compounds, excellent separation capabilities	High	Pharmaceutical stability studies, complex sample analysis[30]

Table 4: Analytical Techniques stability-indicating method (SIM) development

Technique	Sub-Method	Primary Use	Advantages
Chromatographic Techniques	High-Performance Liquid Chromatography (HPLC)	Separation and quantification of APIs and degradation products	High resolution, sensitivity, and reproducibility. Can be coupled with UV-Vis, fluorescence, and MS detectors[35].
	Ultra-High-Performance Liquid Chromatography (UHPLC)	Analysis of complex FDC formulations with multiple APIs	Faster analysis, higher resolution, better sensitivity, reduced solvent consumption[35]
	High-Performance Thin-Layer Chromatography (HPTLC)	Qualitative and semi-quantitative analysis of degradation products	Cost-effective, rapid, low solvent consumption[35]
Spectroscopic Methods	UV-Visible Spectroscopy	Quantification of degradation products absorbing UV/visible light	Simple, cost-effective, and widely used in stability studies[36]
	Fourier Transform Infrared Spectroscopy (FTIR)	Identifying functional groups and structural changes	Non-destructive, identifies oxidation, hydrolysis, and polymorphism[36]
	Nuclear Magnetic Resonance (NMR) Spectroscopy	Structural elucidation of degradation products	Provides detailed molecular structure and degradation pathways[36]
Hyphenated Techniques	LC-MS/MS (Liquid Chromatography-Mass Spectrometry)	Impurity profiling and structural elucidation of degradation products	High sensitivity, specificity, and structural information[37]
	GC-MS (Gas Chromatography-Mass Spectrometry)	Analysis of volatile degradation products	Ideal for oxidative and thermal degradation, detailed mass spectral data[37]
	LC-NMR (Liquid Chromatography-Nuclear Magnetic Resonance)	Separation and structural elucidation of degradation products	Provides both separation and detailed structural insights[37]
	CE-MS (Capillary Electrophoresis-Mass Spectrometry)	Analysis of highly polar and charged degradation products	High resolution for polar compounds, excellent separation capabilities[37]

substances in question or through environmental effects or drug-excipient interactions. This is conversely relevant for formulations with multiple APIs, where some may degrade faster than others.[16]

Regulatory Compliance

Before the approval of a drug, regulatory bodies like FDA, EMA, and WHO require the submission of stability data supported by validated SIMs. ICH Q2 (R1) is the guideline that describes the characteristics required to validate these analytical methods in proving robustness and reproducibility.[17]

Shelf Life Assignment

The SIMs mentioned above facilitate expiry dating of the pharmaceuticals through the assessment of their stability during accelerated and long-term storage.

For Batch-to-Batch Consistency

SIMs are utilized by quality control laboratories to affirm consistent stability properties of drug products across

batches, thereby avoiding any possible differences that could translate into a therapeutic outcome.

Development of Formulations

SIMs also assist in formulating to the extent that they provide information about APIs and excipients susceptible to degradation and therefore assist in selecting stabilizers and/or antioxidants and packaging materials required to enhance product stability.[18]

Techniques Employed to Establish SIM

In the establishment of a stability-indicating method, advanced analytical techniques are applied for the proper separation and identification of degradation products with excellent sensitivity and selectivity. Several instrumental methods are utilized for the development of SIMs, namely, chromatographic methods, spectroscopic methods, or combinations thereof

Chromatographic Techniques

Table 1 summarizing the chromatography techniques used for stability-indicating method (SIM) development.

Spectroscopic Techniques

Spectroscopic methods mentioned in table 2 are employed either as standalone techniques or in combination with chromatography to provide structural information on degradation products.

Hyphenated Techniques

Hyphenated techniques combine two or more analytical methods as given in table 3 to improve separation, detection, and identification of degradation products.

Issues in the Development of FDC Stability-Indicating Methods

The development of stability-indicating methods (SIMs) for FDC formulations is fraught with challenges since they usually contain API(s) that have widely different properties and degradation pathways. Some of the notable challenges are listed below:

API Chemical Interactions

APIs in FDCs may undergo oxidation and hydrolysis to form degradation products. Therefore, it becomes necessary to conduct forced degradation studies for their identification and quantification of such impurities.[31]

Different Degradation Pathways

Each API possesses its pathway for degradation, which will differ from other APIs depending on the conditions given. Thus, forced degradation studies are to be approached carefully to develop a method that will monitor the degradation of all APIs contained in the FDC at the same time.[32]

Choice of a Suitable Analytical Method

The method should be able, to the best extent, to separate APIs from their degradation products and excipients. This may require elaborate analytical techniques such as HPLC, coupled perhaps with MS and NMR, depending on the formulation type and degrading products.[33]

Sensitivity and Specificity

In the method development, it should be guaranteed that the trace detection of degradation products and the distinction of degradation products from APIs and their impurities are well represented. Such detection could be done through detection by advanced methods and applying optimization.

Compliance with Requirements of Regulatory Agencies

Regulatory bodies such as FDA, EMA, and ICH require methods to comply with specifications for certain requirements such as specificity, accuracy, precision, and robustness. The forced degradation study must identify all degradation products, with those exceeding an amount of 0.1% undergoing further toxicity evaluation.[34]

Analytical Techniques Used in the Development of Stability-Indicating Methods

The implication of the above statement is that to develop stability-indicating methods, analytical procedures must be sufficiently sensitive to detect and quantify active pharmaceutical ingredients (APIs) and their degradation products, free from interference by excipients or impurities (Table 4). The choice of an analytical method varies with the drug characteristics, likely degradation routes, complexity of formulation, and regulatory aspects. Overall, the analytical techniques used in the development of SIMs can generally be classified into three broad categories: chromatographic methods, spectroscopic methods, and hyphenated methods. Each of these three types holds its importance concerning the stability

Table 5: Types of stress conditions in forced degradation studies

Stress Condition	Method	Testing Conditions	Examples	Impact on Drug Stability
Acid Hydrolysis (Hydrolytic Degradation)	Expose drug to hydrochloric acid (HCl)	0.1 M to 1 M HCl at 50–80°C for varying durations	Aspirin (acetylsalicylic acid) forms salicylic acid and acetic acid	Drugs with ester, amide, lactone, or lactam groups degrade, resulting in loss of activity
Base Hydrolysis (Hydrolytic Degradation)	Expose drug to sodium hydroxide (NaOH)	0.1 M to 1 M NaOH at similar temperatures as acid hydrolysis	Beta-lactam antibiotics (e.g., penicillins, cephalosporins) undergo hydrolysis	Leads to the loss of antibiotic activity
Oxidative Degradation	Expose drug to oxidizing agents	3% to 30% hydrogen peroxide at room or elevated temperatures	Paracetamol (acetaminophen) forms toxic NAPQI metabolite, Epinephrine forms adrenochrome	Drugs with -OH, -O-, or -SH groups degrade, leading to toxicity or discoloration
Photolytic Degradation (UV and Visible Light Exposure)	Expose drug to UV or visible light	UV light (254 nm or 365 nm) or fluorescent light (≥1.2 million lux hours)	May cause isomerization, oxidation, or free radical formation	Drugs degrade due to light exposure, requiring light protection strategies

Table 6: Advances in Stability-Indicating Method Development

Advancement Area	Description	Key Strategies/Applications	Advantages
Green Analytical Chemistry (GAC) Approaches	Focuses on reducing environmental impact by minimizing hazardous solvent use, energy consumption, and waste production.	- Use of environmentally friendly solvents (e.g., ethanol, water). - Miniaturization of analytical methods (microfluidics, capillary electrophoresis). - Automation and real-time stability monitoring. - Reduction of energy consumption (ambient temperature methods, UPLC).	- Complies with sustainability regulations (ISO 14001, EPA). - Reduces operational costs and toxic waste disposal. - Enhances safety by reducing exposure to hazardous chemicals[47]
Artificial Intelligence (AI) and Chemometric Modeling	AI and ML offer predictive capabilities, automated data processing, and real-time optimization of stability-indicating methods.	- Predictive stability modeling using AI algorithms. - Automated Method Optimization (AMO) for chromatographic conditions. - Real-time data analysis for anomaly detection.	- Reduces experimental workload, making method development faster and cost-effective. - Enhances method robustness by optimizing parameters. - Improves regulatory compliance via data-driven impurity assessment[48]
Capillary Electrophoresis (CE)	CE is a high-resolution, miniaturized separation technique for analyzing highly polar and ionic drugs.	- Separation of difficult-to-analyze drugs like highly polar or ionic compounds. - Chiral separations. - Can be coupled with MS for improved impurity profiling.	- Requires minimal solvents, making it an eco-friendly alternative to HPLC. - Provides high separation efficiency for charged degradation products[49]
Microfluidics and Lab-on-a-Chip (LOC) Technology	Miniaturized platform integrating sample preparation, separation, and detection in a microchip.	- On-chip forced degradation studies for rapid stability screening. - Automated impurity analysis in pharmaceutical production. - Portable devices for real-time stability monitoring.	- Reduces sample volume and reagent usage by over 90%. - Faster analysis times (minutes instead of hours). - High-throughput screening, improving productivity[50]

evaluation of fixed-dose combinations (FDC) formulations to ascertain correct identification and quantification of degradation products.

Forced Degradation Studies in Stability-Indicating Method (SIM) Development

The forced degradation studies, also known as stress testing, are an integral part of the development of stability-indicating methods (SIMs). The degradation studies involve exposing a pharmaceutical formulation to extreme stress conditions in order to hasten the degrading process of active pharmaceutical ingredients (APIs) and capture all possible degradation products. The objective behind forced degradation studies is primarily to profile drug stability, affirm specificity of analytical method, and state compliance with regulatory guidelines such as ICH Q1A(R2) and ICH Q2(R1). Increased complexity in the forced degradation studies is thus introduced in FDC formulations with molecular APIs because of the potential drug-drug and drug-excipient interactions. It is essential to elucidate the degradation pathways of each API under various stress conditions so that formulation strategies can be optimized, including packaging materials and storage conditions, to augment stability for the drug.[38]

Importance of Forced Degradation in Method Validation

Forced degradation studies play a pivotal role in validation of methods referred to as stability-indicating methods (SIMs), so as to establish that the developed analytical method can detect, separate, and quantify active ingredients and their degradation products without interference from excipients. One of the pivotal features of forced studies in SIM development is method specificity. Regulatory guidelines require SIMs to be highly specific, meaning that they must isolate the intact drug from any degradation products. Forced degradation confirms that all degradation products and impurities are resolved from the parent compound, thereby confirming the differentiation of the drug and its breakdown products.

Yet another important benefit is the knowledge of the degradation pathway. Degradation studies are useful in understanding intrinsic stability for APIs and those paths regarding their degradation: hydrolysis, oxidation, photolysis. Such information in formulation optimization and in risk assessments provides cues on likely factors affecting stability of the drug under varying conditions.

Also, forced degradation studies can be termed regulatory compliance. In other words, regulatory authorities like the FDA, EMA, and ICH need to take these steps to have a confirmation of the robustness of every SIM. ICH Q1A(R2) recommends stress testing explicitly for stability profile establishment and appropriate storage conditions and shelf-life specification. With all these conditions fulfilled, the manufacturers substantiate their claim for their products being internationally acceptable and ready for market approval.

The two aspects of impurity profiling and toxicological evaluation are thus fundamental to all forced degradation studies. The identification and specification of degradation products are required to assess potential toxicity. If any degradation product surpasses a permissible limit (generally 0.1%), further toxicological studies are warranted to ascertain safety. This is important to demonstrate that the degradation products do not present a hazard to patients.

Lastly, forced degradation studies serve different purposes for formulation development by providing crucial information on how an active pharmaceutical ingredient degrades under varying stress conditions. Knowledge of this degradation will then aid in the selection of appropriate excipients, stabilizers, and packing materials, thus enhancing drug stability and maintaining its efficacy throughout the shelf life.[39]

Types of Stress Conditions in Forced Degradation Studies

According to ICH Q1A (R2) guidelines, forced degradation studies should expose the drug to a variety of stress conditions detailed in table 5, including hydrolysis (acid/base), oxidation, photolysis, and thermal stress. Each of these conditions mimics possible real-world degradation scenarios.[40]

A Case Study on Degradation Pathways

In explicitly involving a stability-indicating method, the study was focused on the fixed-dose combination (FDC) of metformin and sitagliptin. Stress conditions were applied to the drugs: acid-base hydrolysis, oxidation, photolysis, and thermal degradation. Metformin showed to be stable against oxidative and thermal conditions but degraded under acidic conditions, forming N,N-dimethyl guanylurea as a product. Sitagliptin was found to be light-sensitive, and hydrolysis by-products were formed under acidic and oxidative conditions. HPLC was used as the analytical technique with UV-PDA detection, which provided proof of the specificity of the method.[41]

Regulatory Aspects of Stability-Indicating Method

Development and validation of stability-indicating methods (SIMs) are subject to strict regulations to ensure safety and efficacy and the quality of the drug product during its shelf life. Specific requirements for stability studies, method validation, and impurity profiling have been laid down by these agencies, such as International Council for Harmonisation (ICH), the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA).[42]

Due to the presence of multiple active pharmaceutical ingredients (APIs) that differ in their degradation pathways, stability studies for fixed-dose combinations (FDC) become even more complicated in terms of regulators. Thus, the stability-indicating methods should be selective, robust, and capable of detecting degradation products to meet the regulatory acceptance criteria.

Regulatory considerations regarding stability-indicating methods (SIM) are based broadly on ICH guidelines, specifically ICH Q3B(R2) and ICH Q2(R1). ICH Q3B(R2) provides recommendations for the identification, qualification, and control of degradation products in drug formulations, stressing identification thresholds (≥0.1%), qualification (toxicological studies may be needed if above threshold), and total impurity limits (≤1.0%). Each API in FDCs must be evaluated for degradation separately. Validation of analytical procedures per ICH Q2(R1) ensures specificity, accuracy, and precision, and linearity and sensitivity are addressed by parameters of limit of detection (LOD) and limit of quantification (LOQ). In addition to regulatory agencies, such as FDA and EMA, further expectations are put in place, including full long-term and accelerated stability data, appropriate methods for transferability, peak purity evaluation, and stringent impurity control. Whereas the FDA requires method validation across labs, the agency stresses controlling mutagenic impurities. In the case of EMA, approaches such as bracketing and matrixing, comparative studies on stability, and advanced impurity profiling techniques like LC-MS and NMR are a must for studying biological products.[43]

The acceptance criteria for degradation products are set based on the dosage, toxicity, and classification of impurities for that drug. The level of identification varies with the maximum daily dosage of the active pharmaceutical ingredient (API) from an 0.1% threshold for low-dose drugs (≤1 mg/day) up to 0.2% for more than 100 mg/day of the highest doses. Where degradation products exceed the acceptance limits, they need to be characterized, and where they exceed the qualification threshold, toxicological data need to be provided. Total impurity threshold limits for small-molecule drugs are generally set to an impurity level of ≤1.0% API concentration, whereas more stringent limits (≤0.5%) may be required for highly potent drugs. Regulatory authorities have specified the limits of mutagens and genotoxic impurities, which are 1.5 µg/day for mutagenic impurities as per ICH M7 guideline among others. Genotoxic impurities require further Ames testing, in vitro studies, and overall risk assessment to safeguard the safety of the patients.[44]

Advances in Stability-Indicating Method Development

Over time, the domain of stability-indicating method development has witnessed a remarkable transition due to the ever-increasing technological advancements in analytical methods, introduction of automated systems, and data-driven approach. These aspects have been stated in detail in table 6. Traditional stability-indicating methods are chromato-spectrometrically oriented; in the last decade, recent developments have been geared toward improving existing methods in the area of efficiency, sustainability, and sensitivity, and precision. Emerging trends include green analytical chemistry and AI-driven method optimization, together with cutting-edge tools such as capillary electrophoresis (CE) and, more recently, microfluidics in transforming the pharmaceutical stability sector.[45,46]

CONCLUSION AND FUTURE PERSPECTIVES

Stability-indicating methods (SIMs) are very important and essential to assure safety, efficacy, and regulation of pharmaceutical products. Stability-indicating methods for FDCs would need to be very selective, sensitive, and

rugged because of the complex scenarios they pose, with multiple active pharmaceutical ingredients (APIs) and their degradation pathways. Testing for degradation is performed using traditional methods such as HPLC, UHPLC, and HPTLC, as well as with advanced spectroscopic engagement techniques and separation hyphenated techniques. Future developments will focus on AI-assisted method optimization, in-line stability measurement, green methodologies, multi-component analysis, and hybrid methods. All of these will help promote efficiency and sustainability, as well as compliance with regulatory aspects. SIMs must also fulfill requirements of ruggedness, specificity, selectivity, and economic feasibility, with special regard to regulations imposed by ICH, FDA, and EMA departments. The future prospect for SIMs for the development of FDCs will be automation, sustainability, and cutting-edge technologies towards the safety and long-term stability of pharmaceuticals.

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