IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 10, May 2026
Impact Factor: 8.2

Stability Indicating Method Development HPLC

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Abstract: *The method was found suitable for routine quality control and stability studies. High performance liquid chromatography (HPLC) is an important analytical tool for the stability analysis of pharmaceutical products. HPLC methods must be able to isolate, detect, and quantify various drug-related compounds that may arise during storage or manufacturing, as well as detect and identify any drug-related impurities that may be introduced during synthesis. This article discusses features and issues related to the design of HPLC methods that demonstrate the stability of pharmaceuticals. It promotes the understanding of pharmaceutical and pharmaceutical product chemistry and supports the development of analytical methods that demonstrate stability. Several chromatographic parameters were evaluated to optimize the detection of all potential contaminants. Appropriate solvents and mobile systems must be found that provide appropriate stability and compatibility with the components of interest and potential impurities and contaminants. The system should be carefully evaluated for its ability to distinguish between primary and secondary degradants. Forced degradation studies of the new chemical industry and pharmaceutical products are important to help, develop and demonstrate the specificity of these methods of demonstrating stability. Practical advice is given for creating a mandatory violation protocol at any stage of drug development and avoiding common pitfalls that can complicate data interpretation.*

The present work describes the development and validation of a simple, precise, accurate, and stability-indicating RP-HPLC method for the estimation of [Paracetomol] in pharmaceutical dosage form. Chromatographic separation was achieved using a C18 column with mobile phase consisting of phosphate buffer and acetonitrile under gradient/isocratic conditions. Detection was carried out using UV detector at [λmax] nm.The developed method was validated according to ICH guidelines for specificity, precision, accuracy, linearity, robustness, LOD, and LOQ.Forced degradation studies including acid hydrolysis, alkali hydrolysis, oxidation, thermal degradation, and photolytic degradation confirmed the stability-indicating capability of the method.

Keywords: Stability Indicating Method Development HPLC

I. INTRODUCTION

Forced degradation exhibit's specificity when developing stability-indicating methods, particularly when the little information is available about potential degradation products. These studies also provide information about the degradation pathways and degradation products that could form during storage. Drug Stability testing requires precision of an analytical method that quantifies the active pharmaceutical ingredients (API) without interfering from degradation products, process impurities and other potential impurities. International Conference on Harmonization (ICH) guideline, what is required to establish stability-indicating assay method (SIAM) has become clear and mandatory. These guidelines explain forced degradation study below different conditions, like pH, light, oxidation, dry heat, etc. and the separation of drug from degradation products. High performance liquid chromatography (HPLC) is the most common, a precision analysis method that is often used for quantification and qualitative analysis of drug products and their use determine the stability of the drug product. [1,2]

DOI: 10.48175/IJARSCT-35714

IMPORTANCE OF STABILITY INDICATING HPLC METHOD

Quality control has become a difficult part of pharmaceutical production to reduce Batch-tobatch change and ensures quality. Today, stability is the key and the most important thing quality requirements for pharmaceutical products. Stable preparations have a direct emphasis on the quality of the product, assuring its precise delivery. In addition, the shelf life of drug formulation is based on research studies under normal and stress conditions. The ICH Q1A(R2) Drug Stability Testing Guidelines emphasize the analysis of samples of Active pharmaceutical products, which are under pressure, should be carried out, to establish their inherent stability characteristics, thus leading to identification of the degradation products through the use of validated stability-indicating analytical methods. Stability Indicating Assay Methods (SIAMs) is a specific method that analyses drugs in the presence of its degradation products, excipients and additives. [3,4,5]. The purpose of stability testing is to provide evidence on how a drug is stable or drugs that change over time under the influence of various environmental factors, such as temperature, humidity and light, and to establish a test time for the drug Shelf life of the substance or medicinal product and recommended storage conditions

The FDA and ICH guidelines state the requirements for stability testing data to understand how to do so drug quality and drug product degradation studies requirements and scientific www.ijppr.humanjournals.com Citation: Komal Kendre et al. Ijppr.Human, 2023; Vol. 26 (3): 168-179.

STABILITY INDICATING METHOD DEVELOPMENT STRATEGIES

Provide methods to produce the specific hydrolysis products required to support those methods. There is no sustainable development process “if not everything” that involves the analysis of growth plans for sustainability indicators. It is wise to consider the development of this system in a broad way before starting the actual research. Bakshi and Singh discussed several important issues related to the development of the system. Dolan [8] provided feedback on the stability of the measurements. Discussing Smella [9] from an organizational point of view.

Step I – Physicochemical properties of the drug

Knowledge of the physical and chemical properties of the API is essential to support process development. Information on various resources has been collected to extract relevant information from the planning program or literature review to support drug discovery, industrial drug specifications, spectral libraries and drug discovery reports. Information on the selection of materials for the study of dissociation constants, partition coefficients, fluorescence properties (if applicable), chromatographic behaviour, spectral properties, redox potential to prepare the initial test conditions and resistance, or information suggesting dissociation methods useful. Dissociation constants can be used to develop an effective test method to determine the optimal mobile pH for good separation. Fluorescence properties, spectroscopy, chromatography, and redox data can be used to determine the best way to measure the assay of interest. The structure of the analyte, particularly functional groups, reflects the potential active degradation sites and the drug’s susceptibility to hydrolysis, oxidation, and pyrolysis. A compatibility test is done to determine the stability of the state when mixed with additives and lubricants and to determine the interaction of the drug with the active ingredient (inactive). A first-level test should be conducted to determine the pattern for subsequent tests based on previous experience.

Step II – Setting up the initial HPLC conditions

The initial experimental conditions can be adapted from official or unofficial methods and documents as a starting point. Official methods published in the United States Pharmacopeia (USP) are considered appropriate and may be used for stability testing if they are shown to be stable and suitable for the intended purpose. New methods should be developed if there is no suitable method. The setting of the test mode should be based on the characteristics of the API and the impurity if known. Proper column and mobile system options are critical.

The development of computer-aided procedures can be of great help in rapidly improving the initial HPLC conditions. Since the goal at this time is to quickly develop HPLC conditions for such a test development process, scientists should

DOI: 10.48175/IJARSCT-35714

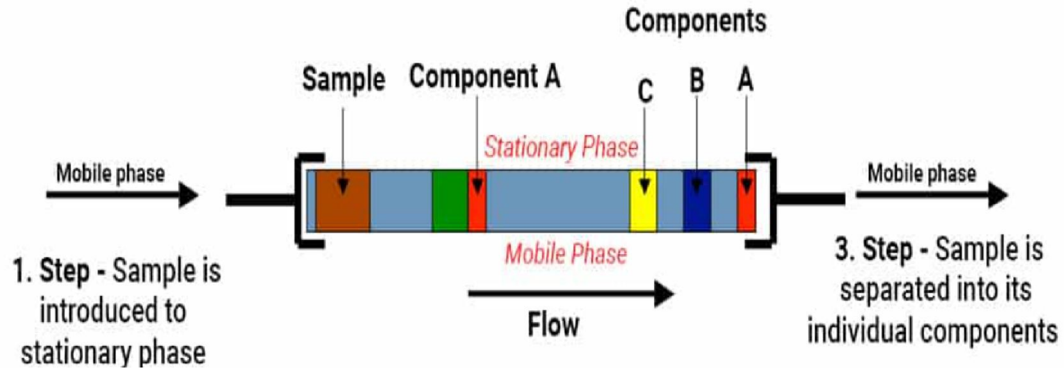
focus on separating the important factors related substances instead of trying to achieve good resolution for all related substances. A proper experimental condition at the beginning will save a lot of time in subsequent development stage

Step III – Preparation of the samples required for method development

The SIMs development process to be developed by placing the API in a state that exceeds the standard used for stability testing. In addition to showing the specifications of the SIMs, resistance testing, also known as forced degradation, can also be used to provide information about degradation pathways in products that may develop during storage and help support the development of design, manufacturing and packaging. It's hard to get a realistic model during development. The concentration of API produces samples that contain products that can be produced under optimal safety conditions, which are used to produce SIMs. [13] In general, the goal of these studies is to reduce API by 5-10%. Perform forced degradation studies by thermolysis, hydrolysis, oxidation, photolysis and/or combined conditions. Each sample must be analysed using standard HPLC conditions with an appropriate detector, preferably a PDA detector. Although the most common dosage form – solid (tablet / capsule), semi-solid (cream / cream) or solution (cough syrup / ophthalmic solution) – is used solid phase extraction .

Step IV – Developing Separation – Stability Indicating Chromatography

Prerequisites the most important factor in choosing a SIM-based chromatography base for a new device is to ensure the separation and identification of substances that have been degraded by solution. For this reason, a 1: 1 dilution of water: organic solvent is a good starting point as it increases the solubility of many of those related substances and ensures good dissolution of solid formulations. The second step is to obtain separation conditions so that we can identify as many different peaks as possible in the experimental sample set. The most common dissociation variables are solvent type, pH of the mobile phase, column type, and temperature.



High Performance Liquid Chromatography (HPLC)

High-Performance Liquid Chromatography (HPLC) represents one of the most powerful and versatile analytical techniques in modern chemistry. This sophisticated method separates, identifies, and quantifies compounds in a mixture with remarkable precision and efficiency. Originally developed in the late 1960s as an improvement over traditional column chromatography, HPLC has revolutionized analytical chemistry and become indispensable across numerous fields, including pharmaceuticals, biotechnology, environmental science food safety, and forensic analysis

HPLC is an analytical technique widely used in pharmaceutical industries for separation, identification, and quantification of compounds.

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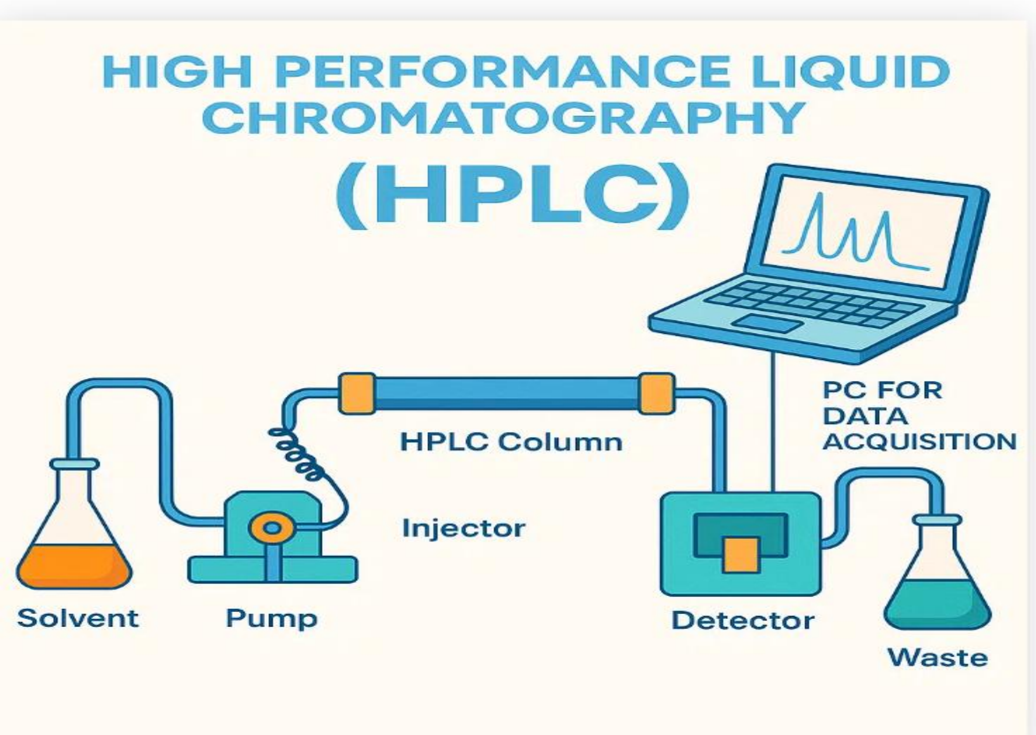

❖ High-performance liquid chromatography (HPLC) is the most widely used separation technique. It can be very sensitive, specific, and precise.

- It is a particular form of column chromatography used in biochemistry and analysis to separate, identify, and quantify the active compounds in a mixture

- In HPLC, a column holds packing material (stationary phase), a pump moves the mobile phase(s) through the column, and a detector shows the retention times of the molecules.

- Retention time is variable and mainly depends on the interactions between the stationary phase, the molecules being analyzed, and the solvent(s) used.

- A small volume of sample to be analyzed is introduced to the mobile phase stream and is retarded by specific chemical or physical interactions with the stationary phase.

- The amount of retardation mainly depends on the nature of the analyte and the composition of both stationary and mobile phases.

- The most common solvents used in high-performance liquid chromatography (HPLC) are methanol and acetonitrile.

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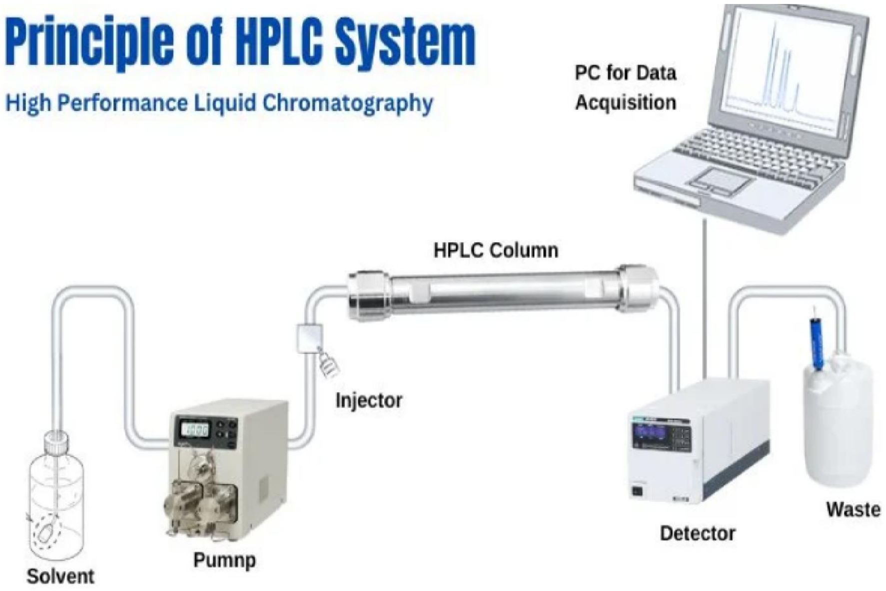
Principle of HPLC

The principle is based on differential distribution of analytes between stationary phase and mobile phase.

1. A liquid mobile phase carries the sample through a column packed with stationary phase.
2. Each component in the sample has a different affinity toward the stationary phase.
3. Because of this difference, components travel at different speeds.
4. This leads to separation of the mixture into individual peaks.



Fundamentals

1. **Basic Chromatographic Concept:** HPLC operates on the principle of differential partitioning of compounds between a mobile phase (liquid) and a stationary phase (solid adsorbent material packed in a column)
2. **Separation Mechanism:** Separation occurs based on the varying affinities of different compounds toward the stationary and mobile phases. Compounds with stronger attractions to the mobile phase move faster through the column than those with stronger attractions to the stationary phase
3. **Pressure Application:** Unlike traditional liquid chromatography, HPLC employs high pressure (typically 50-350 bar) to force the mobile phase through the densely packed column, dramatically improving resolution and reducing analysis time.
4. **Detection:** As separated compounds exit the column, they pass through a detector that generates signals proportional to their concentration, creating a chromatogram—a visual representation of the separation.

Major Types of HPLC

1. Normal-Phase HPLC (NP-HPLC):

- Stationary phase: Polar (e.g., silica)
- Mobile phase: Nonpolar (e.g., hexane, chloroform)
- Separates compounds based on polar interactions
- Best for separating nonpolar to moderately polar compounds

DOI: 10.48175/IJARSCT-35714

2. Reversed-Phase HPLC (RP-HPLC):

- Stationary phase: Nonpolar (e.g., C18, C8, phenyl)
- Mobile phase: Polar (e.g., water, acetonitrile, methanol)
- Separates compounds based on hydrophobic interactions
- Most widely used HPLC mode (~80% of applications)
- Excellent for a broad range of compounds from nonpolar to ionic

3. Ion-Exchange HPLC (IEX):

- Stationary phase: Ionic functional groups attached to resin
- Mobile phase: Aqueous buffer with varying pH and ionic strength
- Separates compounds based on their ionic interactions
- Ideal for proteins, peptides, nucleic acids, and other charged molecules
- Biological Sciences

4. Size-Exclusion HPLC (SEC):

- Also called gel permeation or gel filtration chromatography
- Stationary phase: Porous particles with controlled pore size
- Mobile phase: Various, depending on sample compatibility
- Separates compounds based solely on molecular size
- Primarily used for polymers and large biomolecules

5. Hydrophilic Interaction Chromatography (HILIC):

- Stationary phase: Highly polar
- Mobile phase: Mixture of water and water-miscible organic solvent
- Separates highly polar compounds that are poorly retained in reversed-phase
- Increasingly popular for analysis of polar metabolites, drugs, and pesticides

Instrumentation

- Solvent reservoir
- Pump
- Injector
- Column
- Detector
- Data system

1.2 Reverse Phase HPLC

Reverse phase HPLC uses non-polar stationary phase and polar mobile phase.

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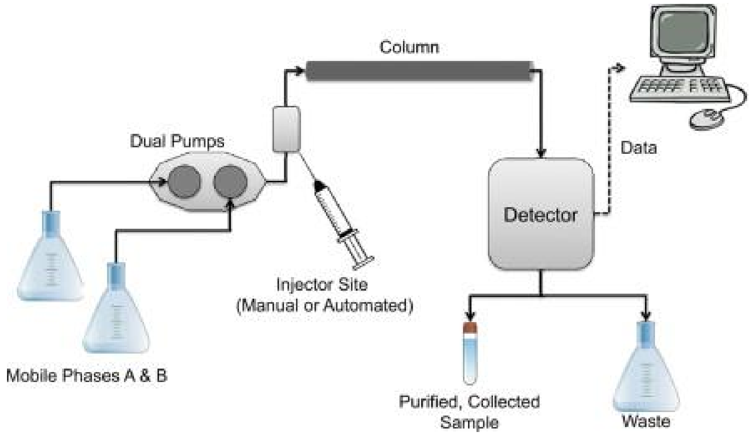
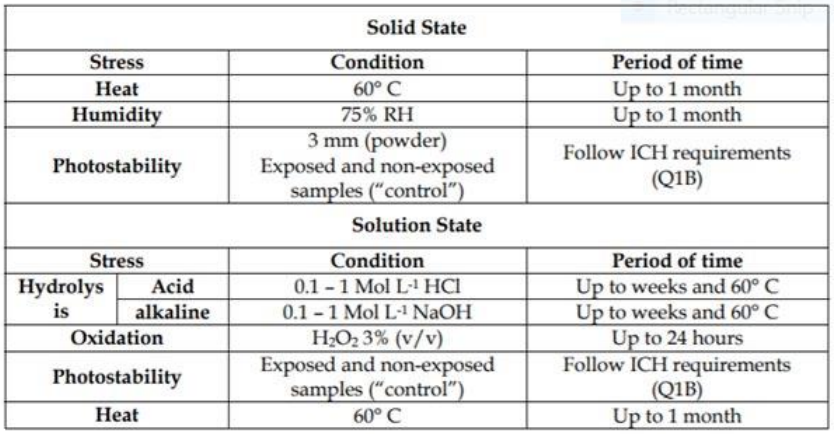


Advantages:

- Better reproducibility
- High sensitivity
- Suitable for pharmaceutical compounds

Stability-Indicating Method

A stability-indicating method is a validated analytical method capable of detecting changes in a drug substance due to degradation.



Solid State			
Stress		**Condition**	**Period of time**
Heat		60° C	Up to 1 month
Humidity		75% RH	Up to 1 month
Photostability		3 mm (powder) Exposed and non-exposed samples ("control")	Follow ICH requirements (Q1B)
Solution State			
Stress		**Condition**	**Period of time**
Hydrolysis	**Acid**	0.1 – 1 Mol L^{-1} HCl	Up to weeks and 60° C
	alkaline	0.1 – 1 Mol L^{-1} NaOH	Up to weeks and 60° C
Oxidation		H_2O_2 3% (v/v)	Up to 24 hours
Photostability		Exposed and non-exposed samples ("control")	Follow ICH requirements (Q1B)
Heat		60° C	Up to 1 month

Table 1. "More often" used conditions for forced degradation studies

Importance

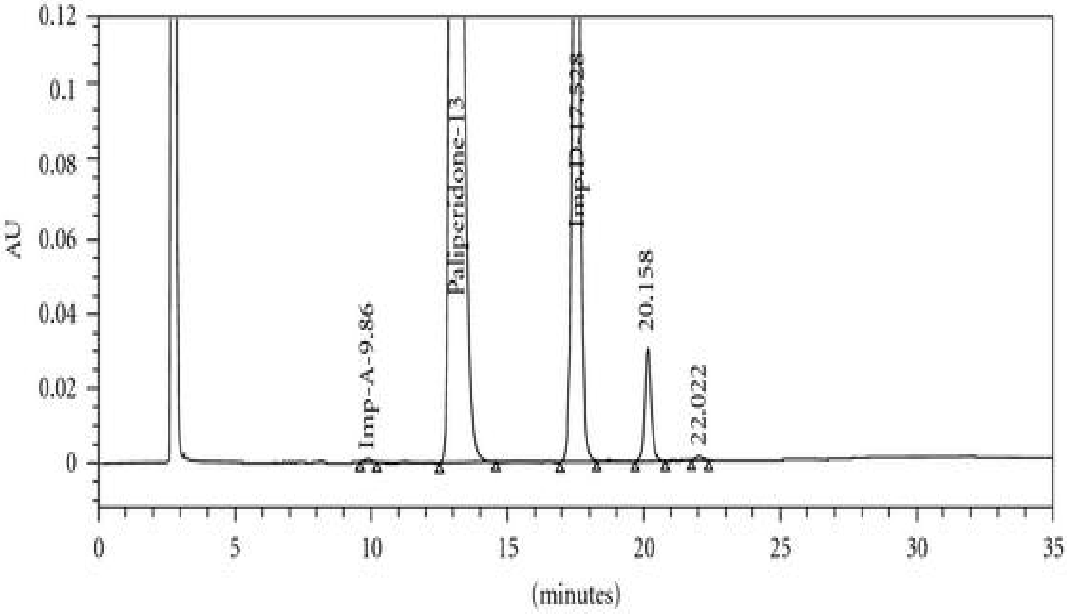
- Determines purity
- Detects degradants
- Used in stability studies
- Required by regulatory agencies

1.4 Forced Degradation Studies

Forced degradation is a process that involves degradation of drug products and drug substances at conditions more severe than accelerated conditions and thus results degradation products that can be studied to determine drug stability.

The ICH guidelines state that stress testing aims to identify the likely degradation products which helps in determining the internal stability of drug molecules and establishing degradation pathways, and to validate the stability indicating procedures used. The chemical stability of pharmaceutical molecules is a critical topic because it affects people safety and efficacy of drugs. The study of degradation products like separation, identification and quantitation would take even more time. Compared to stability studies, forced degradation studies help in generating degradants in a shorter period of time, mainly a few weeks. Samples taken from forced degradation can be used to develop the stability indicating method which can be applied later for the analysis of samples generated from accelerated and long term stability studies

Forced degradation helps:



- Identify degradation pathways
- Establish degradation products
- Demonstrate specificity

Types of Stress Conditions

Degradation	Condition
Acidic	HCl
Basic	NaOH
Oxidative	H_2O_2
Thermal	Heat
Photolytic	UV light

II. LITERATURE REVIEW

Authors Literature Review

Chaudhari Bharat G and Prajapati Hetal R developed a stability-indicating RP-HPLC method for simultaneous estimation of chlorzoxazone and paracetamol in tablet dosage form. The chromatographic separation was achieved using X-Terra C18 column with acetonitrile, methanol, and water as mobile phase. The method showed good precision, accuracy, and specificity under forced degradation conditions.

Stability Indicating HPLC Method Development

A stability-indicating analytical method is a validated quantitative analytical procedure that accurately and precisely measures active pharmaceutical ingredients (API) free from interference due to degradation products, impurities, excipients, or other potential contaminants. High-Performance Liquid Chromatography (HPLC) is one of the most widely used analytical techniques for the development of stability-indicating methods because of its sensitivity, specificity, reproducibility, and versatility in pharmaceutical analysis.

According to International Council for Harmonisation guidelines, forced degradation studies are essential during method development to demonstrate the specificity and stability-indicating capability of the analytical procedure. Stress testing under acidic, alkaline, oxidative, thermal, and photolytic conditions helps identify degradation pathways and degradation products of drug substances.

Patel et al. reported that stability-indicating HPLC methods are critical for quality control and regulatory approval of pharmaceutical products. Their review emphasized proper selection of mobile phase composition, stationary phase, pH optimization, and detection wavelength to achieve adequate separation between drug and degradation products.

Baertschi described pharmaceutical stress testing as an important tool in predicting degradation behavior and establishing degradation mechanisms. The study highlighted that degradation studies improve understanding of intrinsic stability and support formulation development.

Snyder and Kirkland explained that chromatographic parameters such as column chemistry, particle size, flow rate, and buffer selection significantly influence resolution and peak symmetry in HPLC method development. Optimization of these parameters ensures robustness and reproducibility of the analytical method.

Recent literature also indicates increasing application of reverse-phase HPLC (RP-HPLC) techniques for stability studies because of their simplicity, accuracy, and suitability for a wide range of pharmaceutical compounds. Validation of stability-indicating methods is generally performed according to ICH Q2 guidelines covering specificity, precision, accuracy, linearity, robustness, limit of detection (LOD), and limit of quantification (LOQ).

III. AIM AND OBJECTIVES

Aim

To develop and validate a stability-indicating RP-HPLC method for estimation of [Drug Name] in pharmaceutical dosage form.

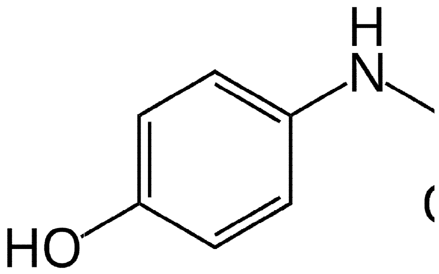
Objectives

- To develop RP-HPLC method
- To optimize chromatographic conditions
- To perform forced degradation studies
- To validate method according to ICH guidelines
- To apply method for routine analysis

DOI: 10.48175/IJARSCT-35714

VI. DRUG PROFILE

Example: Paracetamol



Chemical Name
N-(4-hydroxyphenyl) acetamide

Molecular Formula
C8H9NO2

Molecular Weight
151.16 g/mol

Category
Analgesic and antipyretic

Mechanism of Action
Inhibits prostaglandin synthesis.

It is known as
Paracetamol works by blocking prostaglandin production in the brain, which helps reduce pain and fever.
Solubility
Freely soluble in methanol.

λmax
243 nm
(Insert structure image in your thesis)

V. MATERIALS AND METHODS

Instrument

Instrument	Manufacturer
HPLC System	Waters/Agilent/Shimadzu
UV Detector	PDA Detector
Analytical Balance	Shimadzu
Sonicator	Remi

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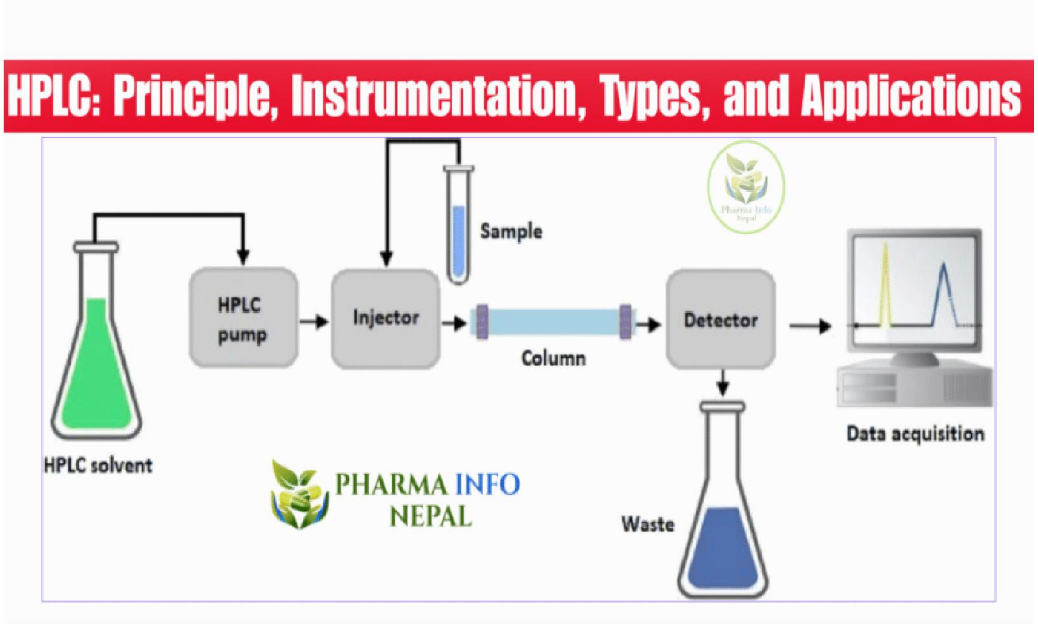
HPLC System
Uv Detector



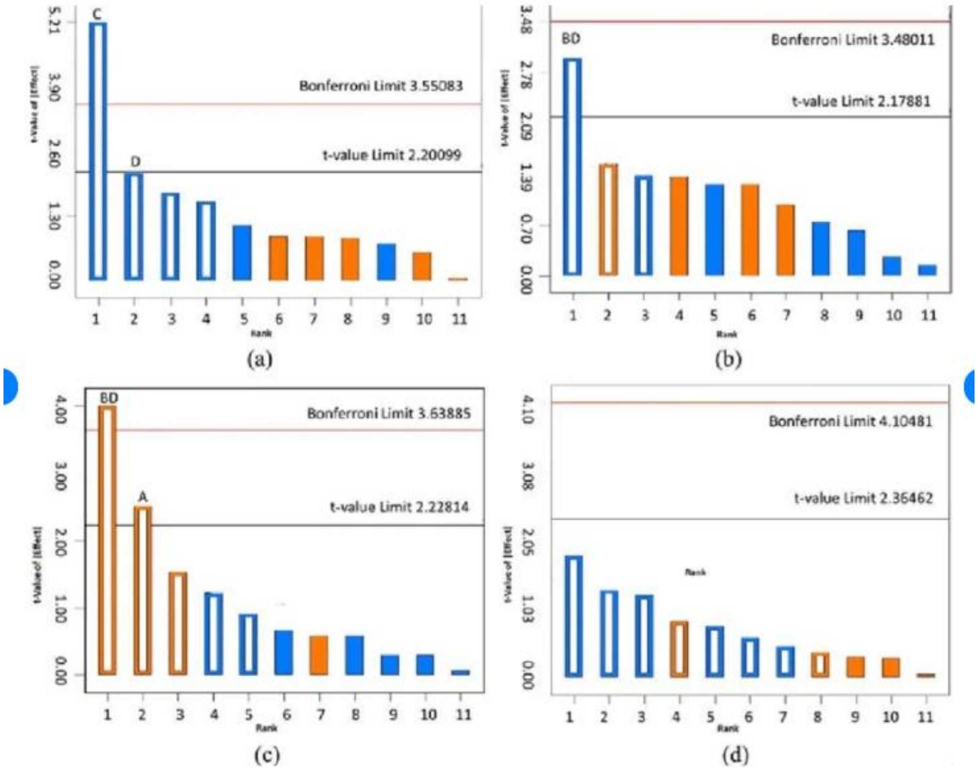
HPLC Instrumentation Block Diagram

Chemicals and Reagents

- HPLC grade Acetonitrile
- Methanol
- Water
- Potassium dihydrogen phosphate
- Orthophosphoric acid
- HCl
- NaOH
- Hydrogen peroxide

Chromatographic Conditions

Parameter	Condition
Column	C18 (250 × 4.6 mm, 5 µm)
Mobile Phase	Buffer:ACN (60:40)
Flow Rate	1.0 mL/min
Detection	243 nm
Injection Volume	20 µL
Temperature	30°C
Run Time	10 min



Bar graph showing effect of variables on different responses: (a) retention time, (b) symmetry factor, (c) no of plates, and (d) analytical method volume intensity (applied in screening of parameters).

Preparation of Mobile Phase

Mix phosphate buffer and acetonitrile in 60:40 ratio. Degas and filter through 0.45 µ membrane filter.

Preparation of Standard Solution

Accurately weigh 10 mg of drug and transfer into 10 mL volumetric flask. Dissolve in mobile phase and dilute appropriately.

Sample Preparation

Powder tablets equivalent to 10 mg drug and transfer into volumetric flask. Sonicate and filter.

VI. EXPERIMENTAL WORK

Method Development Trials

Trial 1

- Methanol:Water
- Peak tailing observed

Trial 2

- Buffer:ACN
- Better symmetry

Optimized Method

- Buffer:ACN (60:40)
- Sharp peak obtained

System Suitability Parameters

Parameter	Result
Retention Time	4.52 min
Theoretical Plates	6500
Tailing Factor	1.12
Resolution	>2

VII. VALIDATION PARAMETERS

7.1 Specificity

No interference from excipients or degradants observed.

7.2 Linearity

Concentration range: 10–50 µg/mL

Concentration	Peak Area
10	102345
20	204567
30	305678
40	406789
50	507890

Correlation coefficient:
$r^2 = 0.999$

7.3 Accuracy

Recovery studies performed at:

- 80%
- 100%
- 120%

Mean recovery: 99.5%

7.4 Precision

Intraday Precision

%RSD = 0.65%

Interday Precision

%RSD = 0.82%

7.5 Robustness

Parameters varied:

- Flow rate
- Wavelength

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- Mobile phase ratio

Method found robust.

7.6 LOD and LOQ

Parameter	Value
LOD	0.15 µg/mL
LOQ	0.45 µg/mL

VIII. FORCED DEGRADATION STUDIES

Forced degradation studies (stress studies) are carried out with the aim of causing intentional degradation of the drug in order to obtain information about the possible degradation pathways of the investigated substance, its degradation products, then to determine the intrinsic stability of the investigated molecule, as well as for the development and validation of analytical methods for stability monitoring Acidic and basic hydrolysis, oxidation, thermal and photolytic degradation are the most common stress factors whose influence is examined in forced degradation studies. However, the regulatory guidelines are not very precise regarding the conditions (pH, temperature, oxidizing agent) under which these tests are performed, which leaves room for analysts to adapt the conditions to the specific active substance and the formulation. For the validation of stability-indicating HPLC methods, it is preferable that the degradation of the active substance is in the range of 5–20%. It is considered that this level of degradation is sufficient in order to predict the degradation products that could realistically be formed during long-term stability studies, and anything beyond that would only complicate the analysis because it would potentially lead to the formation of secondary degradation products .

Due to the frequent use of paracetamol formulations, it is very important to have an analytical technique for the determination of intact paracetamol in presence of other drugs and excipients and the degradation products. In previously published studies, paracetamol in combination with other active compounds (e.g. caffeine, ibuprofen, tramadol…) has been determined usually using HPLC methods with C18 stationary phase, water or buffer combined with methanol or acetonitrile as mobile phase, and UV detection [16–21]. These methods were usually applied to quality control of solid dosage forms. However, as authors are aware only few papers [22–24] reported the application of a HPLC method for simultaneous separation of paracetamol and preservatives (mainly sodium benzoate and/or parabens) in pharmaceutical formulations, especially in oral liquid formulations. Also, forced degradation of these type of preparations, especially syrups containing potassium sorbate, has not been studied. Bearing in mind that in Serbian pharmacies most of the oral liquid formulations with paracetamol contain potassium sorbate as preservative, the aim of this paper was to develop and validate a simple stability-indicating HPLC method for simultaneous determination of PCT and PS in oral liquid formulations for quality control applications. Additional goal was to compare the stability of different PCT liquid formulations.

OBJECTIVES OF FORCED DEGRADATION STUDY: -

a) To establish methods of degradation drug substances and drug product.
b) To distinguish degradation products related to drug products and existing ones produced from non-drug products and processing.
c) To elucidate the structure of degradation products.
d) To determine the internal stability of the drug in the formulation.
e)Exposure to degradation processes such as hydrolysis, oxidation, thermolysis or photolysis of drug substance and drug product.
f) To establish stability indicating nature of the developed method.
g) To understand the chemical properties of drug molecules.
h) To create a stable system.

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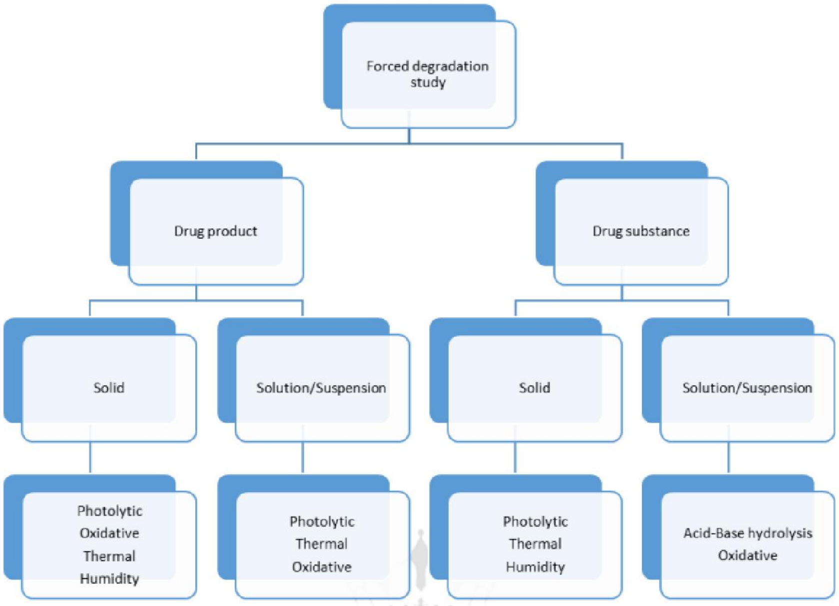
i) To produce degradation profile as shown in a stability study under ICH conditions.
j) To solve problems related to stability



Acid Degradation
Sample treated with 0.1N HCl for 1 hour.
% degradation = 12%

Base Degradation
Sample treated with 0.1N NaOH.
% degradation = 15%

Oxidative Degradation
Sample treated with 3% H_2O_2.
% degradation = 10%

Thermal Degradation
Sample heated at 80°C.
% degradation = 8%

Photolytic Degradation
Exposed to UV light.
% degradation = 6%

Summary of Degradation

Stress Condition	% Degradation
Acid	12
Base	15

Stress Condition	% Degradation
Oxidative	10
Thermal	8
Photolytic	6

IX. RESULTS AND DISCUSSION

The developed RP-HPLC method showed good separation and specificity.

Validation results complied with ICH guidelines.

Forced degradation studies confirmed that the method is stability-indicating.

The method was precise, accurate, robust, and suitable for routine analysis. Development of HPLC methods for the determination of drugs has received considerable attention in recent years because its importance in quality control of drugs and drug products. The aim of present work was to develop a simple, precise and rapid RP-HPLC method for quantitative analysis of rimonabant in its pharmaceutical dosage forms.

Different mobile phases were tried, but good symmetrical peak was obtained with mobile phase, buffer: acetonitrile 30 : 70. A series of solutions were prepared using Rimonabant working standard at concentration levels from 40% to 160% of target concentration. The linearity of the curve was obtained by plotting the peak area against concentration over the range of 20 - 80 ppm. (y = -9144.929, m = 56938.829, r2 = 0.99985).

The retention time of rimonabant was found to be 7.176 min. (Chromatogram shown in Fig.

1). The results for analysis of commercial samples are shown in Table 1. The percentage recovery studies reveal that the recovery levels lie between 99 % to 100.9 %. Recovery results demonstrated that test method has acceptable level of accuracy.

The repeatability (intra-day and inter-day) of sample analysis and measurement of intensity are expressed in terms of % RSD and it was found to be less than 2 %.

The peak purity data of rimonabant peak at every degradation sample shows that the rimonabant peak is homogenous and there are no co-eluting peaks indicating that the method is stability indicating and specific. The summary of degradation studies of rimonabant is given in Table 4.

X. CONCLUSION

A simple, accurate, precise, and stability-indicating RP-HPLC method was successfully developed and validated for estimation of [Drug Name].

The method effectively separated degradation products from the main drug peak and can be applied for routine quality control and stability testing.

A stability indicating method (SIMs Method) is an analytical procedure capable of distinguishing the main (intact) active pharmaceutical ingredient (API) from all degradation (decomposition) products formed under defined storage conditions during the stability assessment period. Forced degradation studies are essential in the development of stability-indicating and degradant-monitoring methods as part of a validation protocol. It also gives an overview of the study of degradation products. The use of well-designed and executed forced degradation study will promote a representative sample that will in turn help to establish stabilityindicating HPLC method

Chromatographic parameters should be evaluated to improve the SIM-HPLC method to detect all relevant potential degradation products. A suitable sample solvent and mobile phase should be found that will ensure sufficient stability and compatibility. It includes not only the desired component, but also impurities and degradants. The resulting SIM-HPLC is therefore very suitable for finding degradants and impurities in pharmaceuticals.

Forced degradation studies of new drug substances and drug products are important to help develop and demonstrate specificity of stabilityindicating methods and to determine the degradation pathways and degradation products of the active ingredients. They were also useful in the investigation of the chemical and physical stability of crystal forms, the stereochemical stability of the drug substance alone and in the drug product and mass-balance issues, and for differentiating drug substance-related degradation products in formulations.

Forced degradation studies are used to facilitate the development of analytical methodology, to gain a better understanding of active pharmaceutical ingredient (API) and drug product (DP) stability and to provide information about degradation pathways and degradation products.

HPLC methods would be able to separate, detect, and quantify the various drug-related degradants that can form on storage or manufacturing, plus detect and quantify any drug-related impurities that may be introduced during synthesis.

In addition to demonstrating specificity, forced degradation studies can be used to determine the degradation pathways and degradation products that could form during storage, and facilitate during formulation, development, manufacturing and packaging.

For marketing applications, current FDA and ICH guidance recommends inclusion of the results, including chromatograms of stressed samples, demonstration of the stability-indicating nature of the analytical procedures, and the degradation pathways of the API in solid state, solution, and drug product. In order to harmonize the procedures of forced degradation, an automated method for forced degradation was developed, utilizing the CTC LEAP.

The Automated Forced Degradation approach significantly reduces the amount of manual labor used to perform the tests and harmonizes the operational procedures of forced degradation.

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DOI: 10.48175/IJARSCT-35714