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A REVIEW ON METHOD DEVELOPMENT AND VALIDATION OF FEXOFENADINE BY DIFFERENT ANALYTICAL TECHNIQUES

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ABSTRACT
Pharmaceutical analysis plays a very prominent role in quality assurance as well as quality control of bulk drugs and pharmaceutical formulations. Rapid increase in pharmaceutical industries and production of drug in various parts of the world has brought a rise in demand for new analytical techniques in the pharmaceutical industries. As a consequence, analytical method development has become the basic activity of analysis. Fexofenadine is an antihistamine commonly used to treat allergy symptoms, including hay fever, conjunctivitis, and skin reactions such as eczema, hives, and reactions to bites and stings. It effectively relieves symptoms like watery eyes, runny nose, sneezing, and itching.

KEYWORDS: Pharmaceutical analysis, Fexofenadine, antihistamine, analytical method development.

INTRODUCTION
Analysis is vital in any product or service, and it is also important in drug because it involves life. Analytical validation for method development and the analysis therapeutic components and associated substances play an important role in the discovery, development and manufacture of pharmaceuticals and natural medicinal compounds. Analytical instruments play a major role in the process to achieve high quality and reliable analytical data. Thus everyone in the analytical laboratory should be concerned about the quality assurance of equipment. Analytical method could be spectral, chromatographic, electrochemical, hyphenated or miscellaneous. Analytical method development is the process of selecting an accurate assay procedure to determine the composition of a formulation. It is the process of proving that an analytical method is acceptable for use in laboratory to measure the concentration of subsequent samples. Analytical methods should be used within GMP and GLP environments and must be developed using the protocols and acceptance criteria set out in the ICH guidelines Q2(R1). Spectrophotometers use a monochromator containing a diffraction grating to produce the analytical spectrum. The grating can either be movable or fixed. If a single detector, such as a photomultiplier tube or photodiode is used. HPLC has many applications in both laboratory and clinical science. It is a technique used in pharmaceutical development to ensure product purity. The components of the sample mixture are separated due to their different degrees of interaction with the adsorbent particles. Its composition and temperature play a major role in the separation. These interactions are physical in nature, such as hydrophobic (dispersive), dipole dipole and ionic, operational pressures is significantly higher, superior resolving power, quantitative analysis of the sample components. A digital RP-HPLC operates on the principle of hydrophobic interactions; another important factor is the mobile phase pH since it can change the hydrophobic character of the analytic. For this reason, most methods use a buffering agent, such as sodium phosphate, to control the pH. Microprocessor and user software control the HPLC instrument and provide data analysis. HPLC separations have theoretical parameters and equations to describe the separation of components into signal peaks when using UV detector or a mass

spectrometer. Liquid chromatography mass spectrometry (LC-MS) is an analytical chemistry technique that combines the physical separation of liquid chromatography (or HPLC) with mass spectrometry (MS). LC separates mixtures with multiple components, MS with structural identity of the individual components with high molecular specificity and detection sensitivity. LC-MS may be applied in a wide range of sectors including biotechnology, environment monitoring, and pharmaceutical, agrochemical, and cosmetic industries. An LC-MS system contains an interface that efficiently transfers the separated components from the LC column into the MS ion source. While the mobile phase in a LC system is a pressurized liquid, the MS analyzers commonly operate under high vacuum (around 10−6 torr / 10−7 "Hg). Overall, the interface is a mechanically simple part of the LC-MS system that transfers the maximum amount of analyte, removes a significant portion of the mobile phase used in LC and preserves the chemical identity of the chromatography products. As a requirement, the interface should not interfere with the ionizing efficiency and vacuum conditions of the MS system. High performance thin layer chromatography (HPTLC) is an enhanced form of thin layer chromatography (TLC). A number of enhancements can be made to the basic method of thin layer chromatography to automate the different steps, to increase the resolution achieved and to allow more accurate quantitative measurements. Automation is useful to overcome the uncertainty in droplet size and position when the sample is applied to the TLC plate by hand. Nowadays, HPTLC has become a routine analytical technique due to its advantages of reliability in quantization of analytes at micro and even in nanogram levels and cost effectiveness.

Analytical method validation

Analytical method validation is the process used to confirm that the analytical procedure employed for a specific test is suitable for its intended use. This validation process provides documented evidence that the performance characteristics of the procedure meet the requirements for the intended analytical applications. In other words, it ensures that the method is fit for its purpose in terms of quality, reliability, and consistency of results.

ICH Method validation parameters

For chromatographic methods used in analytical applications there is more consistency in validation. Related substances are commonly present in the pharmaceutical products but those are always within the limits as specified in ICH (Q2B).

- Specificity
- Linearity
- Accuracy
- Precision
- Limit of Detection
- Limit of Quantitation
- Robustness
- System suitability

Specificity/Selectivity

Specificity is ability to assess unequivocally the analyte in the presence of components that may be expected to be present. The terms selectivity and specificity are often used interchangeably. According to ICH the term specific generally refers to a method that produces a response for a single analyte only while the term selectivity refers to a method that provides responses for a number of chemical entities that may or may not be distinguished from each other. If the response is distinguished from all other responses, the method is said to be selective. Since there are very few methods that respond to only one analyte, the term selectivity is usually more appropriate.

Accuracy

The Accuracy of analytical procedure expresses the closeness of agreement between the value that is accepted either as a conventional true value or as an accepted reference value and value found.

Accuracy may be inferred once precision, linearity and specificity have been established. Accuracy for the area percent method should be established from 50% of the ICH reporting limit to the nominal concentration of drug substance in the sample solution.

Precision

ICH defines the precision of an analytical procedure as the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision is the measure of how close the data values are to each other for a number of measurements under the same analytical conditions. ICH has defined precision to contain three components: repeatability, intermediate precision and reproducibility. Ruggedness as defined in USP XXII <1225>, 1990 incorporates the concepts described under the terms *"intermediate precision", "reproducibility*" and *"repeatability*" of this guide.

Linearity

Linearity of an analytical procedure as its ability (within a given range) to obtain test results that are directly proportional to the concentration (amount) of analyte in the sample.

Limit of detection

Limit of detection (LOD) is the lowest concentration of analyte in a sample that can be detected, but not necessarily qualtitated, under the stated experimental conditions. With UV detectors, it is difficult to assure the detection precision of low level compounds due to potential gradual loss of sensitivity of detector lamps with age or noise level variation by detector manufacturer. At low levels, assurance is needed that the LOD and LOQ limits are achievable with the test method

each time. With no reference standard for a given impurity or means to assure detectability, extraneous peak(s) could "disappear / appear." A crude method to evaluate the feasibility of the extraneous peak detection is to use the percentage claimed for LOD from the area counts of the analyte.

The LOD may be expressed as.

$$\mathbf{LOD = 3.3\ \sigma / S}$$

Where,
σ = Standard deviation of Intercepts of calibration curves.
S = Mean of slopes of the calibration curves.
The slope S may be estimated from the calibration curve of the analyte.

Limit of quantification
Limit of quantitation (LOQ) is the lowest concentration of analyte in a sample that can be determined with acceptable precision and accuracy under the stated experimental conditions.

The LOQ may be expressed as.

$$\mathbf{LOQ = 10\ \sigma / S}$$

Where,
σ = Standard deviation of Intercepts of calibration curves
S = Mean of slopes of the calibration curves
The slope S may be estimated from the calibration curve of the analyte.

Robustness
The robustness of an analytical procedure is defined as a measure of its capacity to obtain comparable and acceptable results when perturbed by small but deliberate variations in specified experimental conditions. Robustness provides an indication of the test method's suitability and reliability during normal use. During a robustness study, conditions are intentionally varied to see if the method results are affected. Example HPLC variations are illustrated for isocratic and gradient methods, respectively.

Examples of typical variations are.
- Stability of analytical solutions
- Extraction time

System Suitability
According to the USP, system suitability tests are an integral part of chromatographic methods. These tests are used to verify that the resolution and reproducibility of the system are adequate for the analysis to be performed. The purpose of the system suitability test is to ensure that the complete testing system is suitable for the intended application.

High Performance Liquid Chromatography (HPLC)
High-performance liquid chromatography (HPLC), formerly referred to as high-pressure liquid chromatography, is a technique in analytical chemistry used to separate, identify, and quantify specific components in mixtures. The mixtures can originate from food, chemicals, pharmaceuticals, biological, environmental and agriculture, etc, which have been dissolved into liquid solutions.

It relies on high pressure pumps, which deliver mixtures of various solvents, called the mobile phase, which flows through the system, collecting the sample mixture on the way, delivering it into a cylinder, called the column, filled with solid particles, made of adsorbent material, called the stationary phase.

Each component in the sample interacts differently with the adsorbent material, causing different migration rates for each component. These different rates lead to separation as the species flow out of the column into a specific detector such as UV detectors. The output of the detector is a graph, called a chromatogram. Chromatograms are graphical representations of the signal intensity versus time or volume, showing peaks, which represent components of the sample. Each sample appears in its respective time, called its retention time, having area proportional to its amount.

HPLC is widely used for manufacturing (e.g., during the production process of pharmaceutical and biological products), legal (e.g., detecting performance enhancement drugs in urine), research (e.g., separating the components of a complex biological sample, or of similar synthetic chemicals from each other), and medical (e.g., detecting vitamin D levels in blood serum) purposes.

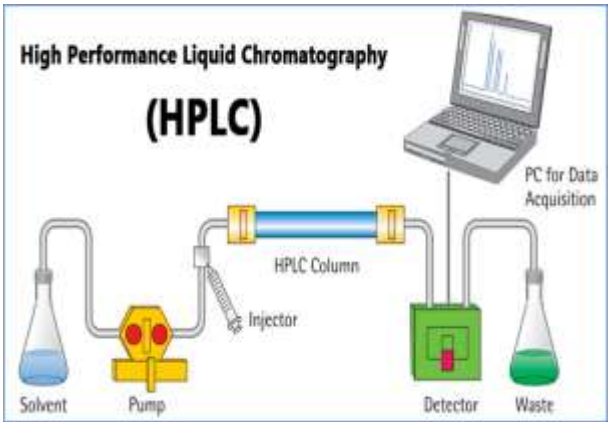


Fig. No.1: High-Performance Liquid Chromatography [HPLC] System.

1 = eluent reservoir
2 = filter
3 = high pressure pump with pulse dampener
4 = pressure gauge
5 = sample injection valve with syringe
6 = column oven
7 = guard column
8 = column
9 = detector
10 = recorder (integrator, PC etc.)

❖ **Liquid chromatography–Mass spectrometry (LC–MS)**

Liquid chromatography–mass spectrometry (LC–MS) is an analytical chemistry technique that combines the physical separation capabilities of liquid chromatography (or HPLC) with the mass analysis capabilities of mass spectrometry (MS). Coupled chromatography - MS systems are popular in chemical analysis because the individual capabilities of each technique are enhanced synergistically. While liquid chromatography separates mixtures with multiple components, mass spectrometry provides structural identity of the individual components with high molecular specificity and detection sensitivity. This tandem technique can be used to analyze biochemical, organic, and inorganic compounds commonly found in complex samples of environmental and biological origin. Therefore, LC-MS may be applied in a wide range of sectors including biotechnology, environment monitoring, food processing, and pharmaceutical, agrochemical, and cosmetic industries.

❖ **Ultra Performance Liquid Chromatography (UPLC)**

Ultra Performance Liquid Chromatography (UPLC) is the newest technology in liquid chromatography based analysis. UPLC is the upgrade high performance liquid chromatography with high pressures, outstanding in both peak resolution and sensitivity. As well as higher sample throughput obtain more available sample information and the decrease separation time consumption. UPLC can provide us with impactful results within their organization. Ultra Performance Liquid Chromatography (UPLC) Based Analysis Services at Creative Proteomics offers you a state-of-the-art liquid separations platform that includes standard UPLC with frequently used separation mechanisms.

❖ **Ultra violet–visible spectroscopy (UV)**

Ultraviolet (UV) spectroscopy or ultraviolet–visible (UV–VIS) spectrophotometry refers to absorption spectroscopy or reflectance spectroscopy in part of the ultraviolet and the full, adjacent visible regions of the electromagnetic spectrum. Being relatively inexpensive and easily implemented, this methodology is widely used in diverse applied and fundamental applications. The only requirement is that the sample absorb in the UV-Vis region, i.e. be a chromophore. Absorption spectroscopy is complementary to fluorescence spectroscopy. Parameters of interest, besides the wavelength of measurement, are absorbance (A) or transmittance (%T) or reflectance (%R), and its change with time.

A UV-vis spectrophotometer is an analytical instrument that measures the amount of ultraviolet (UV) and visible light that is absorbed by a sample. It is a widely used technique in chemistry, biochemistry, and other fields, to identify and quantify compounds in a variety of samples.

UV-vis spectrophotometers work by passing a beam of light through the sample and measuring the amount of light that is absorbed at each wavelength. The amount of light absorbed is proportional to the concentration of the absorbing compound in the sample.

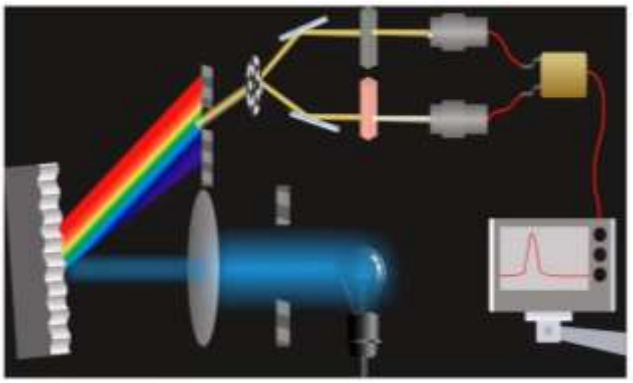
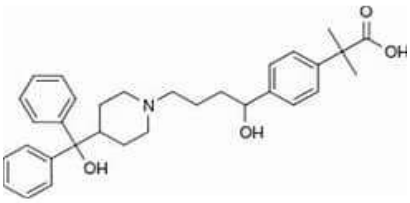


Fig.no. 2: UV Spectroscopy.

DRUG PROFILE

Name: Fexofenadine.

Description: Fexofenadine belongs to a group of medicines called antihistamines. It is used to treat various allergic conditions such as hay fever, conjunctivitis and some skin reactions such as eczema, hives, and reactions to bites and stings. It relieves watery eyes, runny nose, sneezing, and itching.



IUPAC Name: (±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethyl benzene acetic acid.

Chemical formula: $C_{32}H_{39}NO_4$.

Molecular Mass: 501.667 g·mol−¹.

Category: Therapeutically, fexofenadine is a selective peripheral H 1 blocker. It is classified as a second-generation antihistamine because it is less able to pass the blood–brain barrier and cause sedation, compared to first-generation antihistamines.

Mechanism of action: Fexofenadine is an antihistamine that works by selectively blocking peripheral H1 receptors. This blockage prevents the activation of the H1 receptors by histamine, which in turn prevents the symptoms associated with allergies from occurring.

Pharmacodynamics: Fexofenadine is an antihistamine drug that blocks the H 1 -receptor sites on effector cells. It is rapidly absorbed from the GI tract after oral administration, reaching peak plasma levels in about 2 hours. It has a long-lasting effect of up to 12 hours on reducing histamine-induced skin wheal and flare. It does

not cross the blood-brain barrier significantly, resulting in a low potential for sedation.
Absorption: rapidly absorbed from the gastrointestinal tract after oral administration.
Volume of distribution: approximately 5.4-5.8 L/kg.
Protein binding: 60% to 70%
Metabolism: Fexofenadine undergoes very minimal metabolism, with only 5% of an ingested dose being metabolized by the liver. The identified metabolites include a methyl ester of fexofenadine (constituting 3.6% of the total dose) and MDL 4829 (making up 1.5% of the total dose). The specific enzymes responsible for this metabolism have not been fully elucidated.
Route of elimination: Most of the substance is excreted unchanged via the feces (approximately 80%) and urine (around 11–12%).
Half-life: 14.4 hours.
Clearance: The oral clearance of fexofenadine is approximately 50.6 L/h, and the renal clearance is approximately 4.32 L/h.

Toxicity
Safety Profile: Fexofenadine has a favourable safety profile. Even when taken at doses up to 10 times the recommended amount, no cardiovascular or sedative effects have been observed in humans. Research has shown no clinically significant adverse effects compared to a placebo.

Common Side Effects: The most common side effects include headache, drowsiness, nausea, dizziness, and menstrual cramps. However, these are generally mild.

Brand Names: telfast, allegra, fexalergic, fext, stedler, fexogail, fexowish, fexogearv, alfexo, histakem.

Table 1: Solubility studies of Fexofenadine.

SOLVENTS	SOLUBILITY
Water	Slightly Soluble
Methanol	Freely Soluble
Ethanol	Freely Soluble
Chloroform	Slightly Soluble
Acetonitrile	Soluble
Phosphate Buffer	**S**oluble

REVIEW OF LITERATURE

1. **Anil Nishad, (2023):** A simple, sensitive, precise and accurate Reverse phase liquid chromatographic method for the analysis of Fexofenadine Hydrochloride has been developed and validate, This method is used for the determination of compounds in commercial pharmaceutical products. The compounds were well separated on a C18 column [Use Inert silC18, 5µm, 150 x 4.6 mm] utilizing a mobile phase consisting of acetonitrile: phosphate buffer (45:55, v/v, pH 7.0) at a flow rate of 1.0 ml/min with UV detection at 220 nm. The retention time of fexofenadine hydrochloride was found to be 2.05min. With this method linearity was observed (Correlation coefficient = 0.999).
2. **B. Rojarani, et al., (2022):** A simple, accurate, and sensitive method was developed and validated for the determination of Fexofenadine hydrochloride (FEX. HCl) in bulk and tablet formulation. The method is based on the reaction of FEX. HCl with Di cyclohexyl carbodiimide (DCC) and 2-Nitrophenyl hydrazine (2-NPH) in solution, forms 2-Nitrophenyl hydrazide of Fexofenadine hydrochloride. Using ethanol as a solvent, and subsequently measured spectrophotometrically at 415nm. The reaction was extremely rapid at room temperature and absorbance values remained unchanged for at least 24hrs. Beer's law was obeyed in the concentration range of 10-60µg/Ml within the detection limit of 0.62 and 0.68 µg/mL and limit of quantification of 1.88 and 2.06 µg/mL for FEX. HCl bulk and tablet derivatives respectively. The analytical method was validated according to ICH guidelines. The correlation coefficient (r2) was found to be 0.999 and 0.998, % recovery was found to be 100.1 and 99.9, %RSD for repeatability was found to be 1.324 and 0.7824 (intraday), 1.365 and 0.7015 (interday), %RSD for intermediate precision for analyst 1 was found to be 0.435 & 0.520, for analyst 2 %RSD was found to be 0.437 & 0.522 for FEX. HCl bulk and tablet derivatives respectively.
3. **Erten Akbel, et al., (2021):** Fexofenadine belongs to the antihistamine family of drugs. It is used to treat seasonal allergic rhinitis symptoms. In this study, a rapid, simple and sensitive liquid chromatographic method for the quantitative determination of fexofenadine was optimized and validated. Agilent Extend C18 column was used to perform the separation. The optimum chromatographic separation was achieved by the mobile phase consist of acetonitrile and 20 mM KH2PO4 solution (pH 7.5) in 35:65 ratios respectively. The flow rate of 1.2 mL min-1 with a standard retention time of 3.5 min at a wavelength 220 nm was optimized. The developed method has been validated in terms of their linearity, specificity, precision, accuracy, limits of detection and quantification, and robustness as per I.C.H. guidelines. Within a concentration range of 10–60 g mL-1, the correlation coefficient was greater than 0.999. Low relative standard deviation values were obtained in the results of intra-day and inter-day precision tests. The method's accuracy ranged from 99.45 to 100.52 %. The present analytical method can be used to quantify fexofenadine in pharmaceutical preparations.
4. **D. Chinababu, et al., (2021):** A simple, rapid and accurate method was developed for the determination of Fexofenadine Hydrochloride in bulk and pharmaceutical dosage form by RP-HPLC method using C18 column [4.6×250mm,5µm] in binary gradient mode. The mobile phase consisted of methanol and water in the ratio of 80:20 v/v. The

flow rate was maintained at 1.2 mL/min and wavelength was maintained at 220 nm. The column oven temperature was maintained at 40°c. The retention time of Fexofenadine Hydrochloride was attained at 2.96 min. The method was linear over the concentration range from 7.5-40µg/mL and R^2 was found to be 0.999. The intraday and inter day precision %RSD values were obtained <2.0. The LOD and LOQ were attained at 0.603 and 1.829µg/mL respectively. The accuracy results of the method was obtained 98.37-99.84% at different levels of concentrations.

5. **Noushad HS, et al., (2018):** Stability indicating RP-HPLC method was developed and validated for the quantitative determination of Fexofenadine in tablet dosage form. Separation was achieved using an Inertsil ODS-3V column with flow rate of 1.0ml/min using PDA detector and eluents are observed at 245 nm. The mobile phase consisting of 100% methanol. The drug was reacted with the oxidation, hydrolysis, photolysis and thermal degradation. The method was linear over the concentration range of 10-50µg/ml (r2=0.999) with detection and quantification limit of 0.1 µg/ml and 0.4 µg/ml respectively. The method was accurate, precise and robust for the assay of Fexofenadine in pharmaceutical dosage forms.

6. **Katta. Krishna, et al., (2017):** The objective of the research work is to develop suitable analytical method for quantitative determination of Genotoxic impurities at ppm level in Fexofenadine hydrochloride. A single isocratic reversed phase HPLC method was developed on Zorbax RX C-8 column using the mobile phase consists of 0.01M potassium dihydrogen phosphate at Ph-3.0 and acetonitrile in the ratio of 40:60 (v/v) at a flow rate of 1.0 ml/min. The column temperature was maintained at 27°c and UV maximum is 250nm.The limit of detection and limit of quantification of the impurities are established.

7. **Maheen Nafees Khan, et al., (2016):** Fexofenadine Hydrochloride is a piperidine derivative. It is indicated to relieve signs and symptoms that are related with seasonal allergic rhinitis, such as rhinorrhea, sneezing nose, throat and itchy eyes. The aim of study is to establish pharmaceutical equivalence of different brands of Fexofenadine HCl 60 mg film coated tablets available in Karachi, Pakistan. The quality control parameters which are studied are weight variation test, diameter, thickness, disintegration, dissolution and assay specified by British and United State Pharmacopoeia. One-Way ANOVA was applied and results were assessed. Weight variation, Diameter, Thickness and Dissolution results was found to be highly significant among different brands of Fexofenadine Hydrochloride. Weight variation and hardness value requirement was complied by all brands. Disintegration time for all brands was within range i.e. 30 minutes and also complies with the BP/USP recommendation. All brands showed more than 90 % drug release within 45 minutes.

8. **Pallavi M. Sutar, et al., (2015):** The objective of present work was to develop a validated simple, precise, accurate and specific high performance thin layer chromatographic method for estimation of fexofenadine hydrochloride as a bulk drug and in tablet dosage form. The stationary phase used was precoated silica gel aluminium plates 60 F254 with 250 µm thickness. The mobile phase used for separation was toluene: ethyl acetate: methanol: ammonia (30%) (0.5: 7: 3: 0.6; v/v/v/v). The densitometric quantification was carried out at 220 nm. The calibration curve was found to be linear between 1-10 µg/spot.

CONCLUSION

A survey of literature reveals that smart analytical strategies don't seem to be offered for the drug fexofenadine. Despite the fact that only a few strategies of estimation of on top of medicine square measure offered, several of them suffer from one disadvantage or the opposite, like low sensitivity, lack of property and ease etc. the present chemical science strategies square measure inadequate to fulfil the requirements; thence its planned to enhance the present strategies and to develop new strategies for the assay & stability studies of fexofenadine in pharmaceutical dose forms adapting totally different offered analytical techniques like ultraviolet illumination spectrophotometry, HPLC, UPLC and LC-MS.

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CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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