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Review on method development and validation for different pharmaceutical dosage form

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Abstract

Pharmaceutical analysis is crucial for bulk and formulation quality control. Due to global medication manufacturing and pharmaceutical sector expansion, innovative analytical methods are in demand. Developing analytical procedures is now the most significant part of analysis. Improvements in analytical instruments have led to new analytical methods. The improvement of analytical methodologies and technologies has reduced analysis time, increased precision and accuracy, and decreased analysis costs. As a consequence, the majority of pharmaceutical businesses are investing heavily in specialist analysis labs. Analytical techniques for active pharmaceutical ingredients (API), excipients, drug products, degradation products and related substances, residual solvents, and other chemicals are created and verified. As a consequence, it has become an essential component of the regulating organization's standards. Development of analytical methodologies leads to official test methods. Quality control labs utilize these methods to verify drug identity, purity, safety, effectiveness, and performance. Production analytical methods are becoming relevant to regulators. Regulatory agencies expect applicants to demonstrate control of the drug development process using established analytical methodologies.

Keywords: Analytical method development; Validation; Quality control; pharmaceutical dosage form

1. Introduction

Analytical chemistry is a scientific discipline that utilizes advanced technologies to determine the composition of substances through various analytical techniques. We have the capability to deliver both qualitative and quantitative outcomes. Analytical instruments play a crucial role in the attainment of accurate and dependable analytical data. Therefore, it is imperative that all personnel in the analytical laboratory prioritize the assurance of equipment quality [1]. It is imperative that analytical procedures maintain a high level of quality in order to ensure reliable findings and mitigate the risk of unjust legal consequences. The development of methods plays a vital role in ensuring the production of analytical techniques of high quality [2].

It involves the practical application of chemical knowledge, with a particular emphasis on the unique perspective and approach that analytical chemists bring to the study of chemistry. Additionally, it involves enhancing existing analytical techniques, expanding their application to novel sample types, and creating new analytical methods to quantify chemical phenomena, rather than performing standard analyses on regular samples (a task commonly known as chemical analysis) [3]. The selection and development of analytical methods have historically been a significant focus for laboratories operating in the field. However, it is not uncommon for the practical application of these techniques to be

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overlooked or undervalued. Nevertheless, there is a growing trend towards the necessity of showcasing the successful implementation of the method, which is rendering this approach obsolete. Furthermore, analysts will be granted increased autonomy in selecting the analytical method, as long as the chosen method satisfies predetermined criteria [4].

2. Choice of Analytical Method

The selected analytical approach should have all the desirable qualities, with the most crucial being that it should take less time. Analytical techniques should be quick and cost-effective. The accuracy of the analysis in the analytical process must adhere to pharmacopoeia regulations. The method used should be exact and selected. The analytical techniques employed must be both expeditious and cost-effective. Furthermore, the accuracy of the analysis within the analytical process must align with the regulations set forth by the Pharmacopoeia. Therefore, the technique utilized must be precise and carefully selected [5].

3. Instrument Used for Method Development

3.1. High-Performance Liquid Chromatography (HPLC)

High-performance liquid chromatography (HPLC) is an advanced technique employed for the separation of intricate mixtures of molecules present in chemical and biological systems. The separation technique referred to as liquid chromatography has played a pivotal role in the development of high-performance liquid chromatography (HPLC) as it exists today. In the course of the last century, significant progress has been achieved in the domain of chromatography, leading to enhanced efficacy in separation, increased adaptability, and accelerated performance [6].

HPLC offers exceptional specificity and can achieve a high level of precision. Consequently, it is the most commonly employed chromatographic method for analyzing complex drugs. HPLC also plays a crucial role in simultaneously estimating combined dosage forms. The typical detectors employed in HPLC include UV detectors and photodiode array (PDA) detectors [7]. The development of HPLC has enabled LC to achieve great success in providing the following features:

- Velocity of detachment
- Superior resolution
- Keeping an eye on the column's waste water
- Reliable and repeatable analysis
- Analytical process automation

High-performance liquid chromatography (HPLC) is a superior variation of column chromatography that utilizes a pump to apply a great deal of pressure, reaching up to 400 atmospheres, to force the solvent through the column. The adsorbent material, also known as the stationary phase, typically consists of solid particles such as silica or polymers in granular form. The application of pressure in this technique results in significantly increased speed compared to column chromatography. Consequently, it becomes possible to utilize smaller particles as packing material for the column. The utilization of smaller particles leads to a substantially greater surface area, facilitating enhanced exchanges that take place between the stationary phase and the pressurized liquid. The pressurized liquid, commonly referred to as the mobile phase, typically consists of a solvent mixture such as water, acetonitrile, and methanol.The movement of molecules passing by it leads to a more effective separation of the mixture's of HPLC grade. The parts of a mixture are sorted based on their varying levels of interaction with the absorbent particles. As a result, different components elute at different rates and become separate as they exit the column. High-performance liquid chromatography (HPLC) offers significant advantages over column chromatography, including high levels of automation and exceptional sensitivity. [8]. A schematic representation of HPLC Instrumentation illustrated in figure 1.

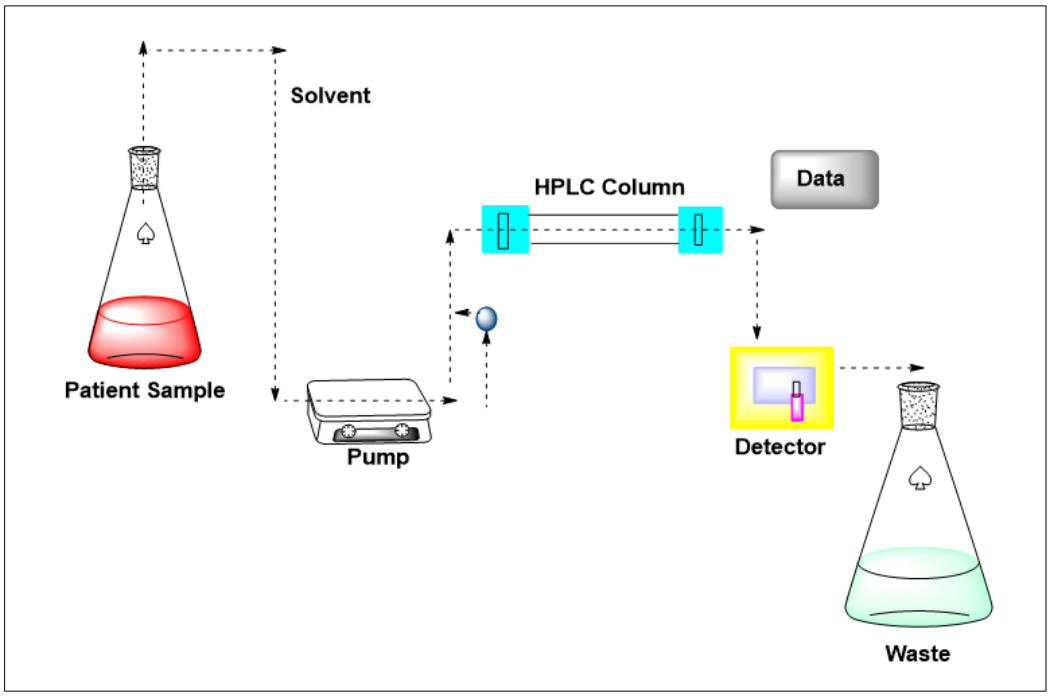

Figure 1 A schematic representation of HPLC Instrumentation

3.2. Reversed Phase Chromatography (RP-HPLC)

Reversed-phase high-performance liquid chromatography (RP-HPLC or RPC) utilizes a stationary phase that is non-polarised and a portable stage that is aqueous and polarity is modest.[9]The utilization of reversed-phase high-performance liquid chromatography (RP-HPLC) is a method employed for the separation of molecules, primarily driven by their water-resistant characteristics. The separation process is dependent on the water-resistant interaction between the dissolvable particles in the active phase and the impairing water-resistant ion in the stationary phase, which is commonly referred to as the sorbent. The dissolvable mixture is initially introduced to the stuff in the presence of a wet screen. Subsequently, the solutes are separated by the addition of organic solvent to the active phase. Absorbance can take place in isocratic situations, characterized by a constant concentration of organic solvent, or through gradient elution, which involves a gradual increase in the amount of organic solvent over time. The elution process facilitates the separation of solutes by exploiting their progressive increase in molecular water resistance. Non-polar molecules undergo a decrease in velocity as they traverse the column. The hydrocarbon groups mostly create different amounts of attraction through van der Waals dispersion forces and hydrophobic interactions. Moreover, these substances demonstrate reduced solubility in the aqueous constituents of the active phase, consequently augmenting their interactions with the hydrocarbon moieties. Reversed-phase high-performance liquid chromatography (HPLC) is widely acknowledged as the prevailing technique in the field of HPLC [8].

RP-HPLC is an exceptionally dominant procedure for drug analysis due to some factors, which include: the great resolution that may be obtained for very closely related compounds as well as structurally very separate atoms across a wide variety of chromatographic settings;

- The manipulation of chromatographic selectivity through modifications in mobile phase characteristics is a relatively straight-forward experimental process.
- The consistently high rates of recovery and subsequent productivity.
- The excellent repeatability of repeated separations performed over a lengthy schedule is partly provided by the sorbent material's stability across a wide variety of moving phase conditions.
- The size of the column remains consistent. The column contains silica particles chemically modified to exhibit non-polar characteristics. The process involves the application of extended hydrocarbon chains, consisting of 8 to 18 carbon atoms, to the surface.
- A polar solvent, such as a combination of water and methanol, is utilized. The polar compounds in the mixture will exhibit enhanced elution through the column due to the pronounced affinity between the polar dissolver and the polar ions within the composition [8].

3.3. Ultra-Performance Liquid Chromatography

Ultra-Performance Liquid Chromatography (UPLC) is an innovative technique that revolutionizes the field of liquid chromatography. It offers significant advancements in three key aspects, namely speed, resolution, and sensitivity. (UPLC) is a highly efficient technique that can be employed for the analysis of particles with a diameter smaller than 2μm [9]. This method offers enhanced resolution, rate, and sensitivity compared to HPLC. In the 21st century, pharmaceutical industries are actively seeking new strategies to enhance efficiency and expedite drug development processes to optimize economic outcomes. The utilization of UPLC analysis has become increasingly prevalent in analytical laboratories as it offers improved product quality. The separation and quantification in (UPLC) are conducted under elevated pressure conditions, reaching up to 100 megapascals (MPa). In contrast to HPLC, it has been observed that UPLC does not demonstrate any adverse effects on the analytical column and leads to reductions in other factors such as rate and solvent consumption, particularly when operating under high-pressure conditions [10].

The primary objectives of the pharmaceutical and chemical industries are to achieve cost reduction in research and enhance the selectivity, sensitivity, and resolution of the detection processes. The purpose can be addressed using the separation technique known as UPLC, a modified version of HPLC. UPLC involves the use of intense pressure and small-sized particles (less than 2 μm) in the column. This results in a shorter column length, leading to time efficiency and reduced solvent consumption. The underlying concept of UPLC is based on the van Deemter assertion, This inquiry seeks to elucidate the relationship between linear velocity and plate height. UPLC offers advantages in terms of speed, resolution, and sensitivity. The aforementioned novel HPLC category employs the same underlying ideas and methodologies, although it exhibits enhanced chromatographic performance. The objective of this study is to provide a comprehensive analysis of the basic aspects, equipment, and applications of ultra-performance liquid chromatography (UPLC) [11].

Application of UPLC:

- The rapid creation of methodologies
- Fast quality control testing.
- Analysis based on numbers.
- Service for method validation of UPLC methodologies.
- Stability testing for pharmaceuticals
- Peptide and glycopeptide mapping can be performed using mass spectrometry detection, specifically utilizing UPLC-MS/MS technology [10].

3.4. UV-Visible spectroscopy

UV-Visible spectroscopy is an investigative technique utilized to quantify the absorption or transmission of distinct wavelengths of UV or visible light by a material relative to a reference or blank sample. The observed strategy of this sample is subject to the influence of its constituents, which has the potential to yield valuable insights regarding the constituents present and their respective concentrations. Since the use of light is essential to the operation of this spectroscopic method, let's start by discussing the characteristics of light.

The amount of energy contained within light is inversely proportional to the distance it can travel. Therefore, light with short wavelengths carries the most power, whereas light with higher wavelengths carries slightly less energy. The process of elevating electrons in a material to a higher-energy state, commonly referred to as absorption, requires a specific level of energy. The electrons located in different bonding sites within a material require varying levels of energy in order to transition to a higher energy state. This explains why light absorbs at different wavelengths in diverse materials. The range of wavelengths that we can detect as visible light as humans spans from around 380 nm (violet) to 780 nm (red). Ultraviolet (UV) light possesses wavelengths that are shorter compared to those of visible light, typically ranging up to approximately 100 nm. The definition of light can be attributed to its wavelength, which is utilized in UV-Vis spectroscopy for the purpose of examining and identifying different compounds. This is achieved by determining the specific wavelengths at which maximum absorption occurs [12].

3.5. High-Performance Thin-Layer Chromatography (HPTLC)

All drug research and development phases often include the analysis of pharmaceutical, natural, and newer medications. One of the convoluted instrumental methods based on the full potential of thin-layer chromatography is high-performance thin-layer chromatography [13]. HPTLC is based on the employment of particular layers composed of tiny particles with a diameter of 5 m that are narrowly dispersed. It is not a unique approach since all the essential parameters, theoretical considerations, and practical components of traditional TLC remain the same. However, because of the subsequent employment of specialized apparatus, HPTLC achieves not just chromatogram downsizing

but also, more crucially, a considerable increase in sensitivity, repeatability, and separation power [14]. A current HPTLC workstation, which includes devices for each chromatographic stage, is software-controlled and produces results comparable to HPLC and GC equipment in terms of excellent manufacture or good laboratory practice [15]. Classification of HPTLC techniques mentioned in figure 2.

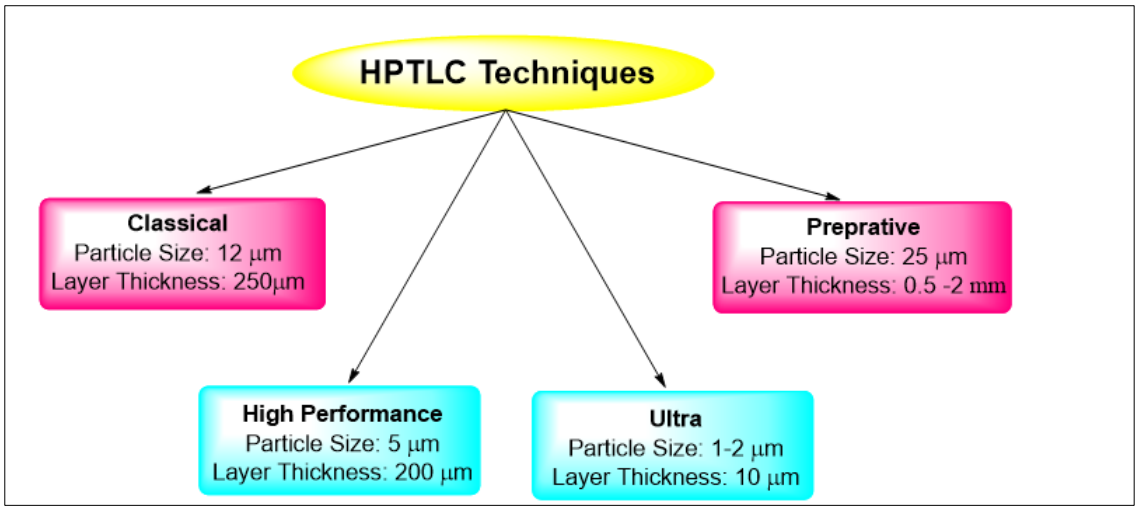

Figure 2 Classification of HPTLC techniques

The advantages of the HPTLC technique are as follows:

- The technique is highly accessible due to its ease of learning and operation. Additionally, the availability of coated plates enhances its efficiency and speed.
- The time required for data interpretation is minimal.
- Reduced analysis time, maintenance costs, and solvent use.
- Simultaneous analysis of qualitative and quantitative data is feasible.
- The range of fixed and movable phases gives this approach many potential applications.
- Fingerprint analysis may be used to check for adulteration, substitution, adulteration purity, and identification.
- Due to its broad applicability, the multicomponent analysis technique has proven highly versatile.
- Permanent documentation can be achieved alongside the chromatogram.
- Post-chromatographic derivatization may be used to analyze materials that do not absorb UV light.
- Filtration and degassing are not necessary for the solvents used in this technique [15].

4. Method Development

A comprehensive analytical procedure has been developed to assess a specific attribute of the substance in question based on predetermined acceptance criteria for the said attribute. When developing a new analytical approach, it is crucial to select the appropriate systematic tools and procedures based on the deliberate purpose and scope of the systematic procedure. Analytical procedure development is fundamentally based on a combination of an automatic understanding of the fundamental steps and previous experience [1].

The process of developing analytical procedures leads to the establishment of officially recognized test methods. Consequently, quality control laboratories have used these methodologies to assess the presentation, recognition, clarity, security, and efficacy of pharmaceutical products. The use of analytical techniques in the manufacturing process has significant importance for regulatory entities. In order for regulatory authorities to grant approval for a medicine, it is necessary for the applicant to exhibit mastery over the entire drug development process through the utilization of officially sanctioned analytical techniques [16].

Following are the different steps which are involve for the Development of New Method

- Characterization of standard analytes
- Method specifications
- The process of method selection

- Preliminary research and instrumentation
- Parameter optimization
- Analytical design documentation
- Sample-based evaluation of the method progress
- Calculating the sample's percent recovery
- Exemplification of statistical methods applied to a sample.

4.1. Method for Estimation of Drug

Various spectro-photometric techniques are used for drug assessment in combined dose forms, including:[18]

- Simultaneous equation method
- Absorption ratio method (Q-ratio method)
- Orthogonal polynomial method
- Derivative spectrophotometry
- Chemical derivatization

4.1.1. Simultaneous Equations Method

When a sample contains two absorbing medications (X and Y), each of which absorbs at the maximum of the other, i.e., 1 and 2, the simultaneous equation approach is employed. If certain conditions are satisfied, it may be able to identify both drugs using this method. The necessary information is (i) X's absorptivity at 1 and 2 and, correspondingly, ax1 and ax2, (ii) absorption of Y at 1 and ay1 and ay2, respectively, (iii) absorbance of the diluted sample at 1 and 2, A1 and A2 respectively. Let Cx and Cy be the amounts of X and Y in the sample that has been watered down. Based on the fact that the absorbance of the mixture is the sum of the absorbances of X and Y at 1 and 2, two formulae are made.

$$\text{At } \lambda 1 \quad A1 = ax1\ bcx + ay1\ bcy \ldots\ldots\ldots (1)$$

$$\text{At } \lambda 2 \quad A2 = ax2\ bcx + ay2\ bcy \ldots\ldots\ldots (2)$$

Rearrange eq. (2)

$$\mathbf{c_y = A_2 - a_{x2}c_x / a_{y2}}$$

Substituting for c_y in eq. (1), and rearranging gives

$$\mathbf{c_x = A_2a_{y1} - A_1a_{y2} / a_{x2}a_{y1} - a_{x1}ay2}$$

and

$$\mathbf{c_y = A_1a_{x2} - A_2a_{x1} / a_{x2}a_{y1} - a_{x1}a_{y2}}$$

Criteria for obtaining maximum precision based on absorbance ratios have been suggested to limit the relative concentrations of the mixture. The criteria are that the ratios,

$$\mathbf{A_2/A_1 / a_{x2} / a_{x1}}$$

and

$$\mathbf{a_{y2}/a_{y1} / A_2/A_1}$$

For the precise determination of Y and X, these ratios should lie outside the range of 0.1-20. These criteria are satisfied only when the λ_{max} of the two components are reasonably dissimilar. An additional measure is that the two components must not interact chemically, negating the initial assumption that the total absorbance is the sum of individual absorbance [18].

4.1.2. Absorbance Ratio Method

Let it be one drug X and Y. According to the Q-Absorption ratio method, use the absorption ratio at two selected wavelengths. One is at an iso-absorptive point, and the other is the λ max of one of the two components. Two equations

were constructed as described below, using the relationship ax1=ay1 at λ1 and L=1. Equations are; At λ1 A1 = ax1Cx + ax1Cy (because ax1=ay1) ……. (1)

At λ2 A2 = ax2Cx + ay2Cy …… (2)

Dividing equation (2) by (1), we get

A2/A1 = (ax2Cx + ay2Cy)/(ax1Cx + ax1Cy) …… (3)

Let Cx/(Cx+Cy)=Fx& Cy/(Cx+Cy)=Fy

Dividing Equation (3) by Cx+Cy, we get

A2/A1 = (ax2Fx+ay2Fy)/(ax1Fx+ax1Fy)

But Fy =1 - Fx A2/A1 = (ax2Fx+ay2-ay2Fx)/ax1 …… (4)

A2/A1 = (ax2Fx/ax1) – (ay2Fx/ ay1) + (ay2/ay1) (because ax1=ay1)

Let ax2/ax1 = Qx, ay2/ay1 = Qy& A2/A1 = QM

So, QM = FxQx – FyQy + QyFx = (QM-Qy)/(Qx-Qy) …… (5)

This equation gives the fraction of the mixture,determining the absolute concentration of X and Y.

Cx/(Cx=Cy) = (A2/A1) -(ay2/ay1)/(ax2/ax1)-(ay2/ay1) ……. (6)

Both equation (5) & (6) gives the fraction, rather than the concentration of X and consequently of Y in the mixture in term of absolute ratio. As these are independent of concentration only approximate rather than accurate. If the absolute concentration of X & Y than rearrange equation (1),

we get

Cx+Cy = A1/ax1…… (7)

From equation (6) & (7), we get

Cx/(A1/ax1) = (QM-Qy)/(Qx-Qy) Cx= {(QM-Qy)/(Qx-Qy)} *(A1/ax1) …… (8)

&

Cy= {(QM-Qx)/(Qy-Qx)}* (A1/ay1) ……..(9)

Finally, equation (8 & 9) gives the absolute concentration value of drug X & Y [19].

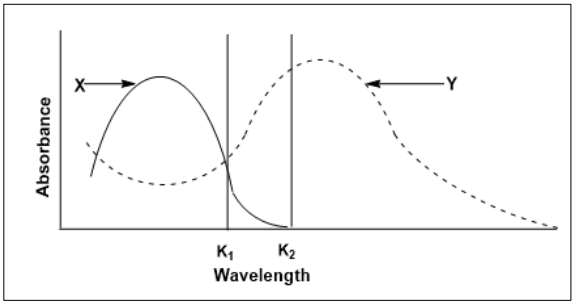

Figure 3 Selection of Wavelengths for Absorbance Ratio Method

4.1.3. Orthogonal polynomial method

The orthogonal polynomial function approach is a mathematical model that was introduced by Glenn with the purpose of removing unnecessary absorption [20]. Choosing the optimal values for the degree of the polynomial, the number of points in the spectrum, and the spacing between the points requires intricate computations. There is software that can make optimizing these settings easier. Two approaches have been reported so far utilizing this program that has been offered [21]. The orthogonal polynomial function approach is a mathematical model used to eliminate unnecessary absorption. This approach relies on the disparity in the spectral profiles of the constituents in a combination within the specified range of wavelengths. The absorption spectrum may be expressed using orthogonal functions, and the contribution to the coefficient of a certain degree of orthogonal polynomial relies on the form of the spectrum and the concentration [22]. Therefore, a quadratic curve will contribute to the coefficients of polynomials of zero degree, first degree, and second degree. On the other hand, a linear curve will contribute to the coefficients of polynomials of zero degree and first degree, but it will not contribute to the coefficients of polynomials of second degree.Thus, the coefficient of second degree polynomial value of sample spectrum, determined from the wavelength range in which one component's spectra is linear and the other is quadratic or cubic, may estimate the second component's content. It may be used to analyze multicomponent samples, however it requires sophisticated calculations to choose the proper degree of polynomial, number of spectrum points, interval between points, and optimization. [23].

4.1.4. Derivative spectrophotometry

The technique of derivative spectroscopy was first introduced in the 1950s due to its wide range of applications. However, its use in practice has been limited due to the complexity involved in generating derivative spectra using UV-visible spectroscopy. During the 1970s, the field experienced a significant advancement with the introduction of microcomputers. This technological development allowed for the generation of derivative spectra more precisely, straightforwardly, efficiently, and consistently. This method was developed to enhance the applicability of the derivative technique. Derivatization of spectra increases selectivity by eliminating spectral interference. Derivative spectroscopy is employed in both qualitative and quantitative studies, wherein it utilizes the first or higher derivatives of absorption with respect to wavelength. The process of spectrophotometric determination of multicomponent formulations can be challenging due to interference caused by the formulation matrix and spectral overlap. There are various approaches available to address these interferences, including the resolution of two simultaneous equations or the utilization of absorbance ratios at specific wavelengths. However, it is important to note that despite these methods, there remains a possibility of obtaining inaccurate results. Additional approaches that can be considered include the use of p-differential least squares and orthogonal function methods.Additionally, the compensation technique can be employed to identify and mitigate undesired or extraneous absorption. Derivative spectrophotometry is a highly useful technique for resolving the spectra of two overlapping substances and effectively eliminating interferences caused by the sample matrix. If a spectrum is represented as absorbance (A)as a function of wavelength(λ) the derivative s spectra are:

Zero order: $A=f(\lambda)$, **First order: A** $=f'(\lambda)$,**Second order: A** $=f''(\lambda)$

The process of derivative spectrophotometry entails the transformation of a standard spectrum into its corresponding first and second (or higher) derivative spectra. In derivative spectrophotometry, the spectrum commonly observed is called the conventional spectrum, also known as the fundamental, zero-order, or D0 spectrum. A first-order derivative refers to the rate of change of absorbance in relation to wavelength. A first-order derivative starts at zero and ends at zero. It also goes through zero at the same wavelength as the absorbance band's maximum value. Either way you look at it, this time there are positive and negative bands, with the most or least at the same wavelengths as the bends in the absorption band [24].

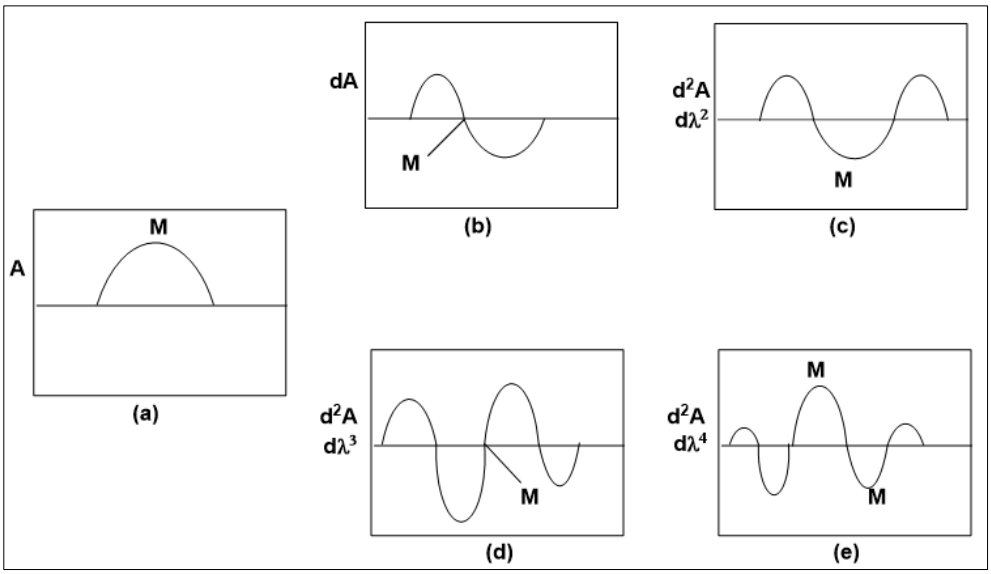

Figure 4 (b)First,(c)Second,(d)Third and I Fourth order Derivative Spectrum of (a)Gaussian peak

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4.1.5. Chemical Derivatization

Chemical derivatization is classified as an indirect spectrophotometric analysis method, in which the target compounds are frequently transformed into those that possess distinct properties. Spectral characteristics. An unusual procedural phase involves the application of surplus reagent to guarantee thorough analyte conversion, thus expanding the achievable dynamic working range. Analytes undergo most chemical derivatization processes to either become species with hyperchromic absorption or to become molecules with longer chromophores, leading to visible-light absorption. For situations where the analyte has weak UV absorption (as is the case with most drugs), interference from irrelevant absorption, a need to increase the procedure's selectivity, or when a colorimetric method would be more cost-effective than a UV-VIS spectrophotometer, chemical derivatization could be used [25].

5. Method Validation

Method validation is a comprehensive field encompassing various parameters for validation, each with distinct approaches tailored to different levels of requirements depending on the intended utilization of the systematic procedure, the instancy of the method enlargement and verification, and the applicable daily standards. An authenticated process may encounter unforeseen or unknown issues during routine usage as its level of confidence is limited. This is because the process was validated based on known or predicted variables. It is essential to validate a method after its development to ensure it meets the requirements and provides a particular level of conviction for its intended use. It is also worth noting that every technique has the potential to fail at some point [17].

5.1. Importance of Validation

- Ensuring the quality of our products and services
- Time-bound
- Optimization of processes
- Cost reduction in quality.
- Issues with nominal mix-ups and bottlenecks
- There is a significant reduction in batch failures, enhancing efficiency and productivity.
- Decrease in the number of rejections. There has been a significant increase in productivity.

- Minimization of capital expenditures
- There has been a decrease in the number of complaints regarding failures related to the process [17].

5.2. Specification and Tests for Method authentication

5.2.1. Specificity/Selectivity

The potential to estimate the sample unambiguously in the absence of factors that may be expected to be available is what the ICH defines as specificity. Typically, this might comprise degradants, matrix, contaminants, etc. [26].

5.2.2. Precision

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Mortal Use (ICH) defines the precision of an analytical procedure. According to ICH, precision refers to the level of agreement or scatter observed among a chain of estimation obtained from a manifold specimen of an equivalent illustrative, all conducted under the specified conditions. Precision can be evaluated at three distinct levels: replicability, central precision, and duplicability. The precision of an inquisitive procedure refers to the level of agreement (degree of variation) among multiple estimations procured from various samples of a compatible specimen under specified conditions.

Precision can be evaluated at three distinct levels

- Repeatability: Expressed as intra-assay precision, it represents the exactness under a comparable operating environment over a short period. A minimum of six duplicates of a comparable or steady sample are set for the 100% examined.
- Intermediate precision: It reflects the correctness inside research labs, on certain days, with specific analysts and particular instruments and equipment. Two distinct analysers create six sample solutions according to the technique provided [26].

5.2.3. Reproducibility

This refers to how closely different testing labs can measure the same thing. Based on the analysis method, each study center set up a total of six sample solutions. Interday and hourly differences (% RSD) were used to figure out how accurate the prochlorperazine maleate (PRO) and betahistine hydrochloride (BET) methods were. For intra-day accuracy, ideal drug solutions within the valuation range were analyzed three times on the same day. Inter-day precision was measured by evaluating drug samples within the reference range for three days over seven days [27].

Reproducibility measures lab accuracy (collaborative studies are usually used to standardize methods). Reproducibility shows how accurate a technique is when different things happen in the lab, like different days, different analysts, different tools, etc. The analysis method says that each place where tests are done can make six sample preparations. Other testing places results are compared to ensure they are statistically the same. Acceptance standards for repeatability are the same as those for middle accuracy [28].

5.2.4. Accuracy and Recovery

The International Council for Harmonization (ICH) defines the accuracy of an analytical procedure. According to ICH, accuracy refers to the degree of agreement between the conventional real value or an expected value and the value obtained. Accuracy can be defined as the degree of agreement between the test results produced by the method and the true value. The accuracy of an investigative process is a measure of how closely the determined value aligns with the accepted true value or reference value. This is commonly referred to as truthfulness." It is essential to ensure that accuracy is established within the designated range of the investigative process. It is recommended to evaluate accuracy by conducting at least nine measurements across a range of concentrations, with a minimum of three concentration levels. For instance, this could involve analyzing three concentrations with three replicates each, encompassing the entire analytical procedure. There are two methods to report the accuracy of the assay. The first method involves expressing it as the percentage recovery of the known added amount of analyte in the sample. The second method involves calculating the deviation between the mean value and the accepted real value and presenting it along with the corresponding confidence interval [29].

5.2.5. Linearity

The International Council for Harmonization (ICH) provides a definition for the linearity of an investigative approach. Linearity, as defined by ICH, pertains to the capacity of a technique to provide test findings that are directly proportional

to the concentration or quantity of the analyte in the sample, within a specific range. The linearity of the test material may be established using two methods: either by directly preparing a standard stock solution or by individually measuring the constituents of the test sample [30].

5.2.6. Range

The range of an analytical procedure, as defined by ICH, is the interval within which the top and bottom absorption amounts of analyte in a sample can be measured with a satisfactory level of precision, accuracy, and linearity. The analytical approach encompasses a spectrum of levels, spanning from the uppermost to the lowermost, which may be determined using the stated method with shown precision, accuracy, and linearity. The range is often expressed in the same units (e.g., %, parts per million) as the test results obtained from the analytical procedure[31].

5.2.7. Limit of Detection

ICH says that the detection limit of a specific analysis method is the smallest amount of analyte in a sample that can be found but not necessarily measured. The limit of detection (LOD) is the point at which a determined number is more significant than the error that comes with it. It is the below-listed number of biomarkers found in a sample but not necessarily measured. People often get the limits of discovery and the method's sensitivity mixed up. A method's sensitivity is how well it can tell the difference between small changes in the concentration or mass of the test sample. In practice, sensitivity is the slope of the calibration curve, which is made by plotting the reaction against the quantity or mass of the sample. This is the smallest amount of an analyte found by chromatographic separation, but that doesn't mean this amount will be an exact number. A blank resolution is introduced, and from blank chromatograms, we have to figure out how much noise there is from peak to peak. Then, figure out the quantity where the information-to-noise ratio is about 3:1.

LOD can be said to be,

$$LOD = 3.3SD/S$$

Where, SD = Standard deviation of response, S = Slope of the calibration curve [32].

5.2.8. Limit of Quantitation

The limit of quantitation (LOQ) is the minimum amount of analyte in a sample that can be accurately and precisely determined using a certain analytical method, as defined by ICH. The quantitation limit is a valuable parameter in quantitative testing for detecting low quantities of chemicals in sample matrices, as it helps to identify contaminants or degradation products. The quantitation limit of an analytical procedure refers to the smallest detectable quantity of analyte in a sample that can be quantified with accuracy and precision. The quantitation limit is a crucial parameter in quantitative tests used to identify minimal amounts of substances in sample matrices. It has a vital function in the identification of pollutants and degradation products. The quantitation limit may be determined using many ways, depending on whether the procedure is non-instrumental or instrumental. Alternative tactics, apart from those outlined in this context, may be effective.

- According to visual evaluation,
- According to the signal-to-noise approach,
- The quantitation limit (QL) may be quantitatively expressed as QL = 10/S, where S represents the slope and is determined based on the standard deviation of the response.
- The variance and standard deviation of the response, denoted as σ, and the slope of the calibration curve, denoted as S, are important variables in this context.
- The value of S can be determined by utilizing the calibration curve of the analyte [33].

6. Conclusion

The creation of analytical procedures is primarily used for the purposes of identification, purification, and, ultimately, the quantification of any substance that may be needed, among other things. The separation and characterisation of impurities as well as deteriorated products, analytical investigations, studies for identification, and ultimately the setting up of parameters that are optimized to particular criteria are the primary activities that are involved in the process of developing an analytical technique. As a result, the important aspects that were outlined in the review article that was just mentioned are of tremendous assistance to an analyst when it comes to estimating pharmaceutical formulations as well as bulk medications.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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