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Original Article

Simultaneous Estimation UV Methods For Multicomponent Drug Formulation: A Review

Taufik Mulla*, Siddheshwar Sonavane, Ayush Tambe, Hitanshi Darji, P. N. Sable

Department of Pharmaceutical Quality Assurance, S.S P. Shikshan Sanstha's Siddhi College of Pharmacy, Chikhali, Pune, Maharashtra 411062, India

ABSTRACT

In the present era, the pharmaceutical market is flooded with a wide range of combination dosage forms, and their number continues to grow rapidly. These multicomponent formulations are gaining significant attention due to their enhanced patient compliance, improved therapeutic efficacy, multiple modes of action, reduced side effects, and faster onset of action. Therefore, it is essential that such formulations comply with established standards of quality, safety, and efficacy. Achieving this requires the availability of reliable analytical techniques for their accurate determination. Various UV spectrophotometric methods are widely employed for the simultaneous analysis of multicomponent formulations. These techniques involve the measurement and mathematical processing of absorption spectra. This review primarily focuses on several important methods, including the simultaneous equation method, difference spectrophotometry, derivative spectrophotometry, absorbance ratio method, derivative ratio spectra method, double divisor ratio derivative method, successive ratio-derivative spectra method, Q-absorbance ratio method, isosbestic point method, absorptivity factor method, dual wavelength method, ratio subtraction method, mean centering of ratio spectra, absorption factor method, and multivariate methods. The theoretical principles and selected applications of these techniques are also discussed.

Keywords: spectrophotometric methods, multicomponent analysis, double divisor, successive ratio-derivative, dual wavelength, ratio subtraction, multivariate methods.

INTRODUCTION

Combination drug products have played an important role in therapeutic practice for many years. When properly formulated, fixed-dose combinations improve patient convenience, reduce treatment costs, and may also enhance therapeutic effectiveness and safety.[1]

The analysis of samples containing multiple components is considered a significant challenge in modern analytical science.[2] Multicomponent analysis has emerged as an important area of interest for analytical chemists in recent years, with wide applications in clinical chemistry, pharmaceutical analysis, and environmental monitoring.[3]

Various analytical techniques are used for multicomponent analysis, including spectrophotometry, chromatography, and electrophoresis. Among these, UV spectrophotometric methods for the simultaneous determination of drugs are particularly highlighted in this review.

Since most analytes in pharmaceutical dosage forms are often present with other compounds that absorb in the same UV spectral region, classical UV spectrophotometric measurements are not suitable for their accurate determination.[4] Traditional methods such as extraction are often difficult to perform because they require large amounts of solvents, which may lead to analyte loss, contamination, or incomplete separation. In addition, these procedures are usually expensive and time-consuming.[2]

UV spectrophotometric techniques are widely used for multicomponent analysis as they reduce the need for complex separation of interfering substances and

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enable the simultaneous determination of multiple analytes, thereby saving both analysis time and cost.[5]

Multicomponent UV spectrophotometric methods involve the recording of absorption spectra followed by mathematical processing for analysis.[6] These methods offer several advantages, including the elimination of prior separation steps such as extraction, concentration of constituents, and cleanup procedures. Spectral data can be easily obtained, and the process is fast, simple, and accurate. These methods are widely applicable to both organic and inorganic systems, with typical detection limits ranging from 10^{-4} to 10^{-5} M and providing moderate to high selectivity.

Different UV spectrophotometric multicomponent analysis methods include :

1. Simultaneous equation method
2. Difference spectrophotometry
3. Derivative spectrophotometry (DS)
4. Absorbance ratio spectra method
5. Derivative ratio spectra method
6. Q-absorbance ratio method

Simultaneous equation method:

If a sample contains two absorbing drugs (X and Y), and each drug absorbs at the λ_{max} of the other, both drugs can be determined using the simultaneous equation method (Vierordt's method), provided that specific conditions are satisfied.

The information required is

- The absorptivities of x at λ1 and λ2, ax1 and ax2 respectively
- The absorptivities of y at λ1 andλ2, ay1 and ay2 respectively
- The absorbance of the diluted samples at λ1 and λ2, A1 and A2 respectively.

Let C_x and C_y represent the concentrations of X and Y, respectively, in the diluted sample. Two equations are then developed based on the principle that, at λ_1, the total absorbance of the mixture is equal to the sum of the individual absorbances of X and Y.

$$A1 = ax1bCx + ay1bCy \ldots\ldots\ldots\ldots (1)$$

$$A2 = ax2bCx + ay2bCy \ldots\ldots\ldots\ldots (2)$$

For measurements in 1 cm cells, b =1cm. Rearrange Eq.(2)

$$Cy = \frac{(A2 - ax2Cx)}{ay2} \ldots\ldots\ldots\ldots (3)$$

Substituting for Cy in eq. (1) and rearranging gives

$$Cx = \frac{(A2ay1 - A1ay2)}{(ax2ay1 - ax1ay2)} \ldots\ldots\ldots (4)$$

$$Cy = \frac{(A1ax2 - A2ax1)}{(ax2ay1 - ax1ay2)} \ldots\ldots\ldots (5)$$

To achieve maximum precision, certain criteria based on absorbance ratios $\frac{A2/A1}{ax2/ax1}$ and $\frac{ay2/ay1}{A2/A1}$

have been proposed, which define the allowable relative concentrations of the components present in the mixture. The criteria state that these absorbance ratios should lie outside the range of 0.1–2.0 to ensure the precise determination of Y and X, respectively. These criteria are satisfied only when the λmax values of the two components are sufficiently different and when no chemical interaction occurs between them, ensuring that the total absorbance remains equal to the sum of the individual absorbances.[7] The simultaneous equation method has been successfully developed for the simultaneous determination of several drug mixtures, such as atenolol with indapamide[8] and dexibuprofen with paracetamol.[9]

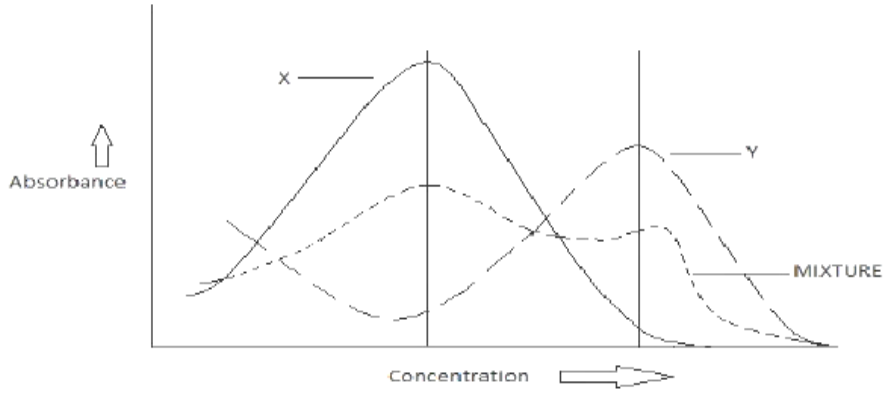

Fig 1: Simultaneous equation method for multi component analysis

Difference spectrophotometry

The selectivity and accuracy of spectrophotometric analysis in samples containing absorbing interfering substances can be significantly improved by difference spectrophotometry. The main principle of this method is the measurement of the absorbance difference (ΔA) between two equimolar solutions of the analyte in different chemical forms, which show distinct spectral characteristics.

The criteria for applying difference spectrophotometry for the assay of a substance in the presence of other absorbing substances are as follows:

1. Reproducible changes should be produced in the analyte spectrum by the addition of one or more suitable reagents.
2. The absorbance of the interfering substances should remain unchanged after the addition of the reagent.

The simplest and most commonly used method for altering the spectral properties of an analyte is the adjustment of pH using aqueous solutions of acids, alkalis, or buffer solutions.

Derivative spectrophotometry (DS)

Derivative spectrophotometry (DS) involves the transformation of a normal spectrum (zero-order or fundamental spectrum) into first, second, or higher-order derivative spectra by differentiating the absorbance of the sample with respect to wavelength (λ).[7] The differentiation of the zero-order spectrum can separate overlapping signals, eliminate background interference caused by other compounds present in the sample,[10] improve the resolution of mixtures by enhancing the detectability of minor spectral features, and increase both sensitivity and specificity.[3]

Derivative spectra provide a more characteristic profile compared to the parent spectrum, showing new maxima and minima along with points where the derivative spectrum crosses the X-axis.[10]

Derivative spectrophotometry follows the basic principles of classical spectrophotometry, such as the dependence of derivative value on analyte concentration and the additivity law. These properties allow the determination of multiple components in a mixture by measuring the derivative spectral amplitude at selected wavelengths. When the derivative peak height of an analyte is measured at wavelengths where the spectra of other components become zero, the measured amplitude depends only on the concentration of that analyte. This method of quantitative analysis is known as the zero-crossing technique.[10] Derivative spectrophotometry has been widely applied for the simultaneous determination of various drug mixtures in pharmaceutical formulations, such as loratadine with pseudoephedrine sulfate,[11] aceclofenac and tramadol with paracetamol,[12] tramadol with ibuprofen[13] or dexketoprofen,[14] paracetamol with tapentadol,[15] naproxen with acetaminophen[16] or diphenhydramine,[17] phenylephrine with ketorolac,[18] and amiloride with hydrochlorothiazide and timolol.[19]

Absorbance ratio spectra method

Consider a mixture containing two compounds, X and Y. The absorption spectrum of the mixture, measured using a 1 cm cell, is represented by the following equation.

$AM = axCx + ayby$ ……..(6)

Where; AM is the absorbance of the mixture,

ax and ay are the molar absorptivities, Cx and Cy are the concentrations of x and y, respectively. If the absorbance of the mixture is divided by the absorbance of a standard solution of x (its absorbance $A°xC°x$) the following equation results

$\frac{AM}{A°x} = \frac{Cx}{C°x} + \frac{Ay}{A°x}$……(7)

The ratio $\frac{Cx}{C°x}$ is a constant value (**Fig. 2**) which can be eliminated by taking the difference in absorbance ratio amplitudes between two wavelengths λ_1 and λ_2 (peak to peak measurement)

$[\frac{AM}{A°x}]_{\lambda1} - [\frac{AM}{A°x}]_{\lambda2} = [\frac{Ay}{A°x}]_{\lambda1} - [\frac{Ay}{A°x}]_{\lambda2}$……..(8)

Equation (8) shows that the amplitude difference in the absorbance ratio of a mixture measured at two wavelengths (λ_1 and λ_2), commonly known as the ratio difference spectrophotometric method, is equal to the amplitude difference of compound y after eliminating the constant interference caused by compound x. The concentration of compound y (Cy) is directly proportional to the peak-to-peak amplitude of its absorbance spectra. A calibration curve is prepared by recording the spectra of different known concentrations of pure y and dividing them by the standard spectrum of pure x (divisor, x°). The peak-to-peak amplitudes at selected wavelengths are then measured and plotted against Cy to obtain the calibration graph. The concentration of compound Y in the mixture is determined using this calibration graph after applying the same procedure to the mixture spectrum. The concentration of compound x is determined in a similar manner. This method has been successfully applied for the simultaneous determination of several binary mixtures, such as emtricitabine with tenofovir[22] and diclofenac with pantoprazole,[21] as well as ternary mixtures like omeprazole, tinidazole, and clarithromycin.[23]

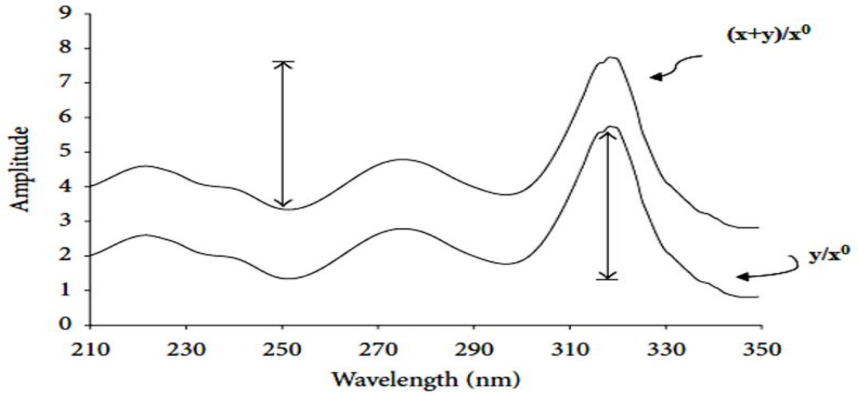

Fig. 2: Ratio spectra of a standard solution of y and a mixture solution (x and y) containing the same concentration of y, using x0 as a divisor.[21]

Derivative ratio spectra method

This simple spectrophotometric method, developed by Salinas et al.,[20] is based on the derivation of ratio spectra for the resolution of binary mixtures. It allows the selection of wavelengths with maximum analytical response, providing better sensitivity and accuracy. This approach enables the determination of active compounds even in the presence of other compounds and excipients that may otherwise interfere with the analysis.[21,24]

The calculation of the first derivative eliminates the constant value $\frac{Cx}{C°x}$ in Equation 9, allowing the concentration of compound y to be accurately determined without interference from the drug x.

$\frac{AM}{A°x} = \frac{Cx}{C°x} + \frac{Ay}{A°x}$……(9)

The difference between the two spectra $\frac{AM}{A°x}$ and $\frac{Ay}{A°x}$ (Fig. 1) is due to the constant interference value due to compound x ($\frac{Cx}{C°x}$). Such interference can be eliminated by measuring the difference in ratio spectra at two selected wavelengths or by calculating the derivative of the ratio spectra.[21] The second derivative of ratio spectra can also be used to improve linearity, enhance mean percentage recovery, and reduce relative standard deviation.[25] The derivative ratio spectra method has been modified for the analysis of ternary mixtures using the derivative ratio spectra zero-crossing method. In this approach, the amplitudes are measured at the zero-crossing points of the derivative ratio spectra for accurate determination.[19, 26-29]

Q-absorbance ratio method

This method, also known as the absorption ratio method, is a modified form of the simultaneous equation method. It is based on the principle that the ratio of absorbance at two selected wavelengths for a substance obeying Beer's law remains constant, regardless of concentration and path length. This constant is known as Hufner's quotient or Q-value. The method involves measuring absorbance at two wavelengths: one at the λmax of one component (λ_2) and the other at the iso-absorptive point (λ_1), where both components have equal absorptivity.[7,9] The concentration of each component is then calculated using mathematical equations.

C_x = (Qm-Qy/Qx-Qy) * A/a_1 ……(10)

C_x = (Qm-Qx/Qy-Qx) * A/a_2 ……(11)

where; Cx and Cy are the concentrations of x and y respectively, A is absorbance of sample at isoabsorptive wavelength and a1 and a2 are the absorptivity of x and y respectively at isoabsorptive wavelength.

$$Qm=\frac{Absorbance\ of\ the\ sample\ solution\ at\ \lambda\ max\ of one\ of\ the\ components(\lambda 2)}{Absorbance\ of\ the\ sample\ solution\ at\ isoabsorpitive\ wavelength}$$

……(12)

$$Qx=\frac{Absorbance\ of x\ at\ \lambda\ max\ of\ one\ of\ the\ components(\lambda 2)}{Absorbance\ of\ xat\ isoabsorpitive\ wavelength}\cdots$$

…….(13)

$$Qy=\frac{Absorbance\ of\ y\ at\ \lambda\ max\ of\ one\ of\ the\ components(\lambda 2)}{Absorbance\ of\ y\ at\ isoabsorpitive\ wavelength}\cdots$$

…….(14)

CONCLUSION

UV spectrophotometric methods have become essential analytical tools for the simultaneous estimation of multicomponent pharmaceutical formulations because of their simplicity, accuracy, rapidity, and cost-effectiveness. These techniques eliminate the need for complicated separation procedures and reduce both analysis time and solvent consumption. Different approaches such as simultaneous equation method, derivative spectrophotometry, absorbance ratio method, derivative ratio spectra method, and Q-absorbance ratio method provide reliable solutions for resolving overlapping spectra and enable accurate quantitative determination of multiple drug components in combined dosage forms. The continuous advancement of mathematical and instrumental techniques has further improved the sensitivity and selectivity of these methods. Owing to these advantages, UV spectrophotometric methods remain highly valuable for routine quality control analysis in pharmaceutical industries and research laboratories, ensuring the safety, efficacy, and standardization of multicomponent drug formulations.

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