

REVIEW

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Ultraviolet spectrophotometric methods for the determination of the minor component presented in fixed-dose pharmaceutical combinations through the last two decades (2000–2020)

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Abstract

Background: The pharmaceutical industry and the National Regulatory Authorities are now focusing on the quantification of multi-component drugs for quality control testing.

Main body: Recently, the utilization of the ultraviolet spectrophotometric methods has become vital for the analytical studies for the routine analysis of different fixed-dose combination products either in the presence of a minor component in their combination or not. This article reviewed several published methods to those that have been applied to quantify some pharmaceutical combinations containing minor components through the last two decades.

Conclusion: The applied spectrophotometric methods are labor, time-saving, and also considered a cheap substitute for the overpriced high-performance liquid chromatographic technique.

Keywords: Fixed-dose combinations drug, Minor component, Ultraviolet spectrophotometric methods

Background

For over 100 years, researchers have been investigating and evaluating the impacts of the fixed-combination medications which have the potential of increased effectiveness, decreased toxicity, and decreased drug resistance; thus, it has become a standard for the treatment of many diseases [1].

The benefits of fixed-dose pharmaceutical combinations are well acknowledged, and there has been a dramatic increase in the activities of the pharmaceutical industry to supply a new drug combination, which challenges the quality control to determine their multiple analytes in several presented ratio regardless of how

different drug concentrations differ from each other, as there are some combinations in where the concentration of one of the two drugs is high (major component) where the concentration of the second drug is very small (minor component). The minor component is pointed according to its ratio in the mixtures as well as its absorptivity at different wavelengths so this is leading to a challengeable spectral banding which hindered their simultaneous determination.

Main text

Mathematical ultraviolet spectrophotometric analytical methods have appeared overwhelmingly in the last few years and have replaced the other chromatographic ones to a pronounced degree [2]. This can be due to their usability, less time and solvent usage, lack of prior extraction or separation steps, and lower cost of the course

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Table 1 Examples for applications of ultraviolet spectrophotometric methods for the determination of the minor component presented in different fixed-dose pharmaceutical combinations

Method	Mixture	Pharmaceutical combination	Ref
Methods based on signal enhancing			
Zero-crossing derivative	Chlorpheniramine maleate (CP), phenylephrine HCl (PE) and phenylpropanolamine HCl (PP)	Tablet dosage form, labeled to contain (CP, 2 mg; PE, 5 mg, and PP, 20 mg) per one tablet	[7]
	Omeprazole (OMP), tinidazole (TIN), and doxycycline (DOX)	Capsules dosage form, labeled to contain 20 mg (OMP), 500 mg (TIN), 50 mg (DOX) per one capsule	[8]
Area under the curve correction	Ofloxacin (OFX), prednisolone acetate (PA) and tetryzoline HCl (TZH) with benzalkonium chloride (BNZ).	Eye drops, labeled to contain 3 mg of OFX, 2 mg of PA, 0.4 mg of TZH, and 0.05 mg of BNZ per 1 mL	[9]
Chemometric methods			
Continuous wavelet transform as a pre-processing tool in partial least-squares	Drotaverine (DRO), caffeine (CAF), paracetamol (PAR), and p-aminophenol (PAP, the major impurity of PAR)	Tablet dosage form, labeled to contain 40.0 mg of DRO, 400.0 mg of PAR, and 60.0 mg of CAF per one tablet	[10]
Partial least-squares	Bromhexine (BRM) and cotrimoxazole	Tablets dosage form labeled to contain cotrimoxazole and BRM per one tablet in ratio of (100:1) (in weight)	[11]
	Sulfamethoxazole (SMX) and trimethoprim (TMP)	Oral suspension dosage form, labeled to contain 400 mg SMX, and 80 mg TMP per 5 mL in ratio (5:1)	[12]
Partial least squares with regression model updating	Chloramphenicol (CPL) and dexamethasone sodium phosphate (DSP) with benzalkonium chloride (BNZ)	Eye drops, labeled to contain 5 mg CPL, 1 mg DSP, and 0.1 mg BNZ per 1 mL	[13]
Artificial neural networks (ANN)	Paracetamol (PAR) and orphenadrine citrate (ORN)	Tablet dosage form, labeled to contain PAR, and ORN in ratio (14:1) per one tablet	[14]
Methods based on geometrical relationship of standard addition			
H-Point standard addition	Paracetamol (PAR) and diclofenac sodium (DCL)	Tablet dosage form, labeled to contain (PAR 250 mg + DCL 50 mg) per one tablet in ratio (5:1)	[15]
Ratio H-point standard addition	Tetryzoline HCl (TZH) with ofloxacin (OFX) and prednisolone acetate (PA) with benzalkonium chloride (BNZ)	Eye drops, labeled to contain 3 mg of OFX, 2 mg of PA, 0.4 mg of TZH, and 0.05 mg of BNZ per 1 mL in ratio of (7.5:5:1)	[16]
	Metoclopramide hydrochloride (MET) with aspirin (ASP)	Sachets Each sachet contains 10 mg MET, 1620 mg lysine acetylsalicylate (which was equivalent to 900 mg ASP), and aspartame in ratio of (1:90)	[17]
	Sodium Cromoglicate (SCG) Tetryzoline HCl (TZH) with benzalkonium chloride (BNZ)	Eye drops, labeled to contain 40 mg of SCG, 0.5 mg of TZH, and 0.1 mg of BNZ per 1 mL in ratio (80:1)	[16]
-Geometrical amplitude modulation -Geometrical induced amplitude modulation	Tetryzoline HCl (TZH) with ofloxacin (OFX) and prednisolone acetate (PA) with benzalkonium chloride (BNZ)	Eye drops, labeled to contain 3 mg of OFX, 2 mg of PA, 0.4 mg of TZH, and 0.05 mg of BNZ per 1 mL	[16]
	Sodium cromoglicate (SCG) Tetryzoline HCl (TZH) with benzalkonium chloride (BNZ)	Eye drops, labeled to contain 40 mg of SCG, 0.5 mg of TZH, and 0.1 mg of BNZ per 1 mL	[16]
Methods based on geometrical relationship of blank subtraction			
Derivative compensation ratio	Sodium cromoglicate (SCG) and xylometazoline hydrochloride (XYLO)	Nasal drop, labeled to contain 2% SCG and 0.025% XYLO per 100 mL	[18]
Compensated area under the curve	Tetryzoline HCl (TZH) with Ofloxacin (OFX) and prednisolone acetate (PA) with benzalkonium chloride (BNZ)	Eye drops, labeled to contain 3 mg of OFX, 2 mg of PA, 0.4 mg of TZH, and 0.05 mg of BNZ per 1 mL	[9]
Methods based on ratio spectra			
Ratio difference	Pseudoephedrine hydrochloride (PSE) and ibuprofen (IBU)	Tablet dosage form, labeled to contain 30 mg of (PSE), and 200 mg of (IBU) per one tablet	[19]
	Sodium cromoglicate (SCG) and fluorometholone (FLU)	Ophthalmic solution, labeled to contain, SCG and FLU in ratio of (20:1) per 1 mL	[20]
	Chloramphenicol (CPL) and dexamethasone sodium phosphate (DSP) with benzalkonium chloride (BNZ)	Eye drops, labeled to contain 5 mg CPL, 1 mg DSP, and 0.1 mg BNZ per 1 mL	[13]

Table 1 Examples for applications of ultraviolet spectrophotometric methods for the determination of the minor component presented in different fixed-dose pharmaceutical combinations (*Continued*)

Method	Mixture	Pharmaceutical combination	Ref
Ratio subtraction coupled with extended ratio subtraction	Sodium cromoglicate (SCG) and fluorometholone (FLU)	Eye drops, labeled to contain 20 mg of SCG and 1 mg of FLU per 1 mL	[21]
Ratio subtraction	Ciprofloxacin (CIP) and fluocinolone acetonide (FLU)	Single-dose otic solution labeled to contain CIP and FLU in a ratio of (CIP: FLU) (12 : 1) per 1 mL	[22]
	Omeprazole (OMP), tinidazole (TIN), and doxycycline (DOX)	Capsule dosage form, labeled to contain 20 mg (OMP), 500 mg (TIN), 50 mg (DOX) per one capsule	[8]
	Flumethasone (FP) pivalate and clioquinol (CL)	Ear drops labeled to contain 0.2 mg of FP and 10 mg of CL per 1 mL	[23]
Extended ratio subtraction	Ciprofloxacin (CIP) and fluocinolone acetonide (FLU)	Single-dose otic solution labeled to contain CIP and FLU in a ratio of (CIP: FLU) (12 : 1) per 1 mL	[22]
Derivative ratio	Pseudoephedrine sulphate (PSE), loratadine (LOR), and paracetamol (PAR).	Tablet dosage form claimed to contain 120 mg of PSE, 5 mg of LOR, and 500 mg of PAR per one tablet	[24]
-Double divisor ratio spectra -Derivative -Area under curve of derivative ratio -Successive -Derivative of ratio spectra	Ofloxacin (OFX), prednisolone acetate (PA), and tetryzoline HCl (TZH) with benzalkonium chloride (BNZ)	Eye drops, labeled to contain 3 mg of OFX, 2 mg of PA, 0.4 mg of TZH, and 0.05 mg of BNZ per 1 mL	[9]
Derivative ratio-zero crossing	Omeprazole (OMP), tinidazole (TIN), and doxycycline (DOX)	Capsule dosage form, labeled to contain 20 mg (OMP), 500 mg (TIN), 50 mg (DOX) per one capsule	[8]
Successive derivative ratio	Omeprazole (OMP), tinidazole (TIN), and doxycycline (DOX), ofloxacin (OFX), prednisolone acetate (PA), and tetryzoline HCl (TZH) with benzalkonium chloride (BNZ)	Capsule dosage form, labeled to contain 20 mg (OMP), 500 mg (TIN), 50 mg (DOX) per one capsule	[8]
	Eye drops, labeled to contain 3 mg of OFX, 2 mg of PA, 0.4 mg of TZH, and 0.05 mg of BNZ per 1 mL	[9]	
Constant center	Pseudoephedrine sulphate (PSE), loratadine (LOR), and paracetamol (PAR).	Tablet dosage form, labeled to contain 120 mg of PSE, 5 mg of LOR, and 500 mg of PAR per one tablet	[24]
	Omeprazole (OMP), tinidazole (TIN), and doxycycline (DOX)	Capsule dosage form, labeled to contain 20 mg (OMP)/500 mg (TIN)/50 mg (DOX) per one capsule	[8]
	Sodium cromoglicate (SCG) and fluorometholone (FLU)	Eye drops, labeled to contain 20 mg of SCG and 1 mg of FLU per 1 mL	[21]
Amplitude modulation	Ciprofloxacin (CIP) and fluocinolone acetonide (FLU)	Single-dose otic solution labeled to contain CIP and FLU in a ratio of (CIP: FLU) (12 : 1) per 1 mL	[25]
	Chloramphenicol (CHL), dexamethasone sodium phosphate (DXM), and tetryzoline hydrochloride (TZH) with benzalkonium chloride (BNZ)	Eye drops, labeled to contain 5 mg of CHL, 1 mg of DXM, 0.25 mg of TZH, and 0.02 mg BNZ per 5 mL	[13]
-Amplitude summation -Absorption subtraction	Chloramphenicol (CHL), dexamethasone sodium phosphate (DXM), and tetryzoline hydrochloride (TZH) with benzalkonium chloride (BNZ)	Eye drops, labeled to contain 5 mg of CHL, 1 mg of DXM, 0.25 mg of TZH, and 0.02 mg BNZ per 5 mL	[13]
-Absorptivity centering -Extended ratio subtraction	Ciprofloxacin (CIP) and fluocinolone acetonide (FLU)	Single-dose otic solution labeled to contain CIP and FLU in a ratio of (CIP: FLU) (12 : 1) per 1 mL	[22]
Derivative subtraction coupled with constant multiplication	Chloramphenicol (CPL) and dexamethasone sodium phosphate (DSP) with benzalkonium chloride (BNZ)	Eye drops, labeled to contain 5 mg CPL, 1 mg DSP, and 0.1 mg BNZ per 1 mL	[13]
Mean centering	Flumethasone pivalate (FP) and clioquinol (CL)	Ear drops labeled to contain FP and CL in ratio of (1: 50) (FP: CL) per 1 mL	[23]
Continuous wavelet transform	Ofloxacin (OFX), prednisolone acetate (PA), and tetryzoline HCl (TZH) with benzalkonium chloride (BNZ)	Eye drops, labeled to contain 3 mg of OFX, 2 mg of PA, 0.4 mg of TZH, and 0.05 mg of BNZ per 1 mL	[16]
	Drotaverine (DRO), caffeine (CAF), paracetamol (PAR), and p-aminophenol (PAP, the major impurity of PAR)	Tablet dosage form, labeled to contain 40.0 mg of DRO, 400.0 mg of PAR, and 60.0 mg of CAF per one tablet	[9]

Method based on spectrum addition and methods based on sample enrichment by spiking or spectrum addition technique

Spectrum addition	Ciprofloxacin (CIP) and fluocinolone acetonide (FLU)	Single-dose otic solution labeled to contain CIP and	[22]
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Table 1 Examples for applications of ultraviolet spectrophotometric methods for the determination of the minor component presented in different fixed-dose pharmaceutical combinations (Continued)

Method	Mixture	Pharmaceutical combination	Ref
Sample spiking	Sodium cromoglicate (SCG) and xylometazoline hydrochloride (XYLO)	FLU in a ratio of (CIP: FLU) (12:1) per 1 mL.	[18]
	Canagliflozin (CAG) and metformin (MEF)	Nasal drop, labeled to contain 2% SCG and 0.025% XYLO per 100 mL	
		Tablet dosage form, labeled to contain 10 mg (CAG) and 100 mg (MEF)	[26]

[3–6]. In this review, the ultraviolet spectrophotometric methods are classified in dealing with the minor component in five different spectral manipulation pathways as follows:

Methods based on spectral signal enhancing process

These methods involve the two techniques namely area under the curve (AUC) and derivative, where AUC can be easily calculated using spectra manager program and it has the advantage of increasing the sensitivity since the value belongs to AUC is greater than the absorbance value for the same substance, even in lower concentrations, also it can be applied either in zero-order spectrum or in the derivative spectrum. However, in case of having a component with an unspecified peak in the zero-order absorption spectrum, the derivative technique is a better solution which gives a derived spectrum with identified peaks which also derivative that can be used to improve overlapped spectra resolution, but it has the disadvantage of rising signal to noise ratio and requires specifying some parameters of the derivative process [7–9].

Methods based on obtaining the hidden spectral information of the minor component by spectro-chemometric tools

Chemometrics and spectrophotometer are a powerful combination method for obtaining the hidden spectral information in spectral data and for improving robustness, analytical frequency, and practicality for analytical methods. However, this technique could not be applied without a special program like Matlab®. It is anticipated that the spectro-chemometric methods can provide a fast-quantitative study of the pharmaceutical dosage forms [10–14].

Methods based on evaluating the geometrical relationship of standard addition or blank subtraction

Where in standard addition technique, different concentrations of minor component (x) are added to the binary mixture (x,y), and then, the obtained regression equation from the geometric representation of signal versus C_x is used to determine $C_{x\text{minor}}$ in the mixture. This technique has the advantage of utilizing several standard solutions which minimize the error in determining component

concentration. The second case of geometric representation depends on placing different concentrations of the minor component in the reference cell and then recording mixture solution (x,y) against each reference cell, in order to obtain a linear representation of signal versus different reference cells. These methods succeeded in determining the minor compound without any interference with the major one, but they demand many experiments to construct the geometric representation of signal against (C_{minor}) [15–18].

Methods based on ratio spectra

These methods handle with ratio spectra by different strategies like subtraction, multiplication, factor calculation, mean centering, and derivative in order to resolve the interference between the components in the mixture, and in many cases, these methods have the ability of determining each component in zero-order, so we could get the spectral profile of each component, and that acts as a fingerprint determination. This ability gives these methods a great advantage over the other ones because they cannot only determine the compounds in the mixture, but also eliminate interference with excipients that exhibit UV absorbance and that may hinder the determination of the components of the mixture [19–25].

Methods based on sample enrichment by spiking or spectrum addition technique

These methods are the best choice when the concentration of the minor component is deviating from Beer's law which happens in the situation of low concentrations where the process of determining this compound by smart spectrophotometric methods becomes impossible without utilizing these techniques which increase the concentration of the minor component to fall within the linearity of the developed method. The first technique depends on adding known concentrations of a pure minor component to the pharmaceutical preparation before proceeding the developed methods and then subtracting the added concentration before calculating the claimed concentration of the minor component by the developed methods [18]. The second method utilizing spectrum addition instead of sample spiking to increase the concentration of the minor component by adding a standard spectrum of a pure minor component

Table 2 Advantages and disadvantages of ultraviolet spectrophotometric methods for the determination of the minor component presented in different fixed-dose pharmaceutical combinations

Methods	Advantages	Disadvantages
Methods based on signal enhancing		
Zero-crossing derivative	-Raises resolution of overlapped spectra in binary mixture.	-Amplifies signal to noise ratio. -Demands choosing a suitable wavelength increment for proceeding derivative -Demands selecting zero-crossing point.
Area under the curve correction	-Raises sensitivity, more than absorption correction method -Easier calculations than traditional (AUC)	-Requires extended spectrum of one of the components than the other.
Chemometric methods		
Continuous wavelet transform as a pre-processing tool in partial least-square	Collects more analytical data from the full matrix spectrum of drugs mixture tested, enabling each component in the mixture to be calculated successfully.	Several steps were required to complete the separation process successfully. The need to special software (Matlab)
Partial least-squares (PLS)	In PLS, both the data in the absorption matrix and the concentration matrix are used and this provides a more stable model as it eliminates noise from both absorption and concentration data.	Need Matlab program connected with UV-spectra device
Partial least squares with regression model updating	Considered as a robust analytical method despite spectral data noise and missing data.	Need Matlab program connected with UV-spectra device
Artificial neural networks (ANN)	Obtaining the relationships between independent variables, allowing all drugs to be calculated in extended nonlinear range.	Need Matlab program connected with UV-spectra device
Methods based on geometrical relationship of standard addition		
H-Point standard addition	-Determines binary mixture with large difference in its components signal	-Required choosing two wavelengths where the interfering component has the same absorbance -Many graphical representations and tests are needed
Ratio H-point standard addition	-Determines binary mixture with large difference in its components signal -No need for any considerations upon selecting the wavelengths	-Required normalized spectrum for division
Geometrical amplitude modulation	-Applicability to partial and sever overlapped spectra	-The need of iso-absorption point or extended spectrum of the major component. -The need of normalized spectrum for division -Many tests are needed.
Geometrical induced amplitude modulation	-Applicability to partial and sever overlapped spectra -No need for iso-absorption point or extended spectrum of the major component.	The need of normalized spectrum for division - Many tests are needed
Methods based on geometrical relationship of standard addition		
Compensated area under the curve	-Determines binary mixture with large variance in its components	-Calibration curve is required for every mixture

Table 2 Advantages and disadvantages of ultraviolet spectrophotometric methods for the determination of the minor component presented in different fixed-dose pharmaceutical combinations (Continued)

Methods	Advantages	Disadvantages
Derivative compensation ratio	<p>signal</p> <ul style="list-style-type: none"> -Determines binary mixture with large variance in its components signal -Raises resolution of overlapped spectra in binary mixture 	<ul style="list-style-type: none"> -Calibration curve is needed for every mixture -Needs for choosing a suitable wavelength increment for proceeding derivative
Methods based on ratio spectra		
Ratio difference	Cancels derivative step which improve signal to noise ratio	<ul style="list-style-type: none"> -Requires tests to choose the best concentration for dividing. -The need of standard spectrum of the interfering substance for the dividing process
Ratio subtraction	-Regains the zero order spectra of the interfering substances	<ul style="list-style-type: none"> -Require extended spectrum of one of the components than the other -Incapables to determine the extended component
Derivative ratio-zero-crossing	-Applies to determine compounds in ternary mixture	<ul style="list-style-type: none"> -Requires tests to choose the best concentration for dividing. -Needs standard spectrum of interfering substance for the dividing process -Needs selecting zero-crossing point
Derivative ratio	<ul style="list-style-type: none"> -Applies to determine compounds in ternary mixture. -No necessity for zero-crossing point 	<ul style="list-style-type: none"> -Requires tests to choose the best concentration for dividing -Needs choosing a suitable wavelength increment for proceeding derivative -Needs standard spectrum of the interfering substance for the dividing process.
Double divisor ratio spectra derivative	<ul style="list-style-type: none"> -Applies to determine compounds in ternary mixture. -No necessity for zero-crossing point 	<ul style="list-style-type: none"> -Requires tests to choose the best concentration for dividing -Needs choosing a suitable wavelength increment for proceeding derivative. -Needs standard spectrum of the two interfering substances for the dividing process
Area under curve of derivative ratio	<ul style="list-style-type: none"> -Cancels interference of the major compounds -Raises sensitivity 	<ul style="list-style-type: none"> -Requires tests to choose the best concentration for dividing -Needs standard spectrum of the interfering substance for the dividing process
Successive derivative of ratio spectra	-Applies to determine compounds in ternary mixture	<ul style="list-style-type: none"> -Requires extended spectrum of one of the components in the ternary mixture - Requires tests to choose the best concentration for dividing. -Needs standard spectrum of the interfering substance for the dividing process

Table 2 Advantages and disadvantages of ultraviolet spectrophotometric methods for the determination of the minor component presented in different fixed-dose pharmaceutical combinations (*Continued*)

Methods	Advantages	Disadvantages
Extended ratio subtraction	-Regains the zero order spectra of the interfering substances	-Requires extended spectrum of one of the components -Un appropriate for determining low concentrations of the more extended substance -Needs standard spectrum of the none extended substance for the dividing process spectrum as a divisor -Requires tests to choose the best concentration could be used as a divisor
Constant center	-Regains the zero order spectra of the interfering substances -Applicability to partial and sever overlapped spectra	-Needs standard spectrum of the interfering substance for the dividing process -Requires tests to choose the best concentration for dividing
Amplitude modulation	-Eliminates the step of selecting the best divisor concentration. -Getting the concentration of both substances by one regression equation	-Requires extended spectrum of one of the components -The need of normalized spectrum for dividing process
Absorption subtraction	-Getting the concentration of both substances by one regression equation	-Demands the calculation of absorption factor.
Amplitude summation	-The drafts in the isosbestic point in derivative step may able to correct interference from some additives	-Demands the calculation of response factor. -Amplifies signal to noise ratio. -Requires choosing a suitable wavelength increment for proceeding derivative
Absorptivity centering	-Regains the zero order spectra of the interfering substances -Applicability to partial and sever overlapped spectra	-Demands the calculation of two factors -The need of normalized spectrum for dividing process -Requires many steps to apply it
Derivative subtraction coupled with constant multiplication	-Regains the zero order spectra of the interfering substances	-Requires extended spectrum of one of the components -Requires tests to choose the best concentration for dividing
-Constant multiplication coupled with spectrum subtraction	-Regains the zero order spectra of the interfering substances	-Requires extended spectrum of one of the components -Requires standard solutions of the interfering compound to be used as a divisor. -Requires tests to choose the best concentration could be used as a divisor
Constant center coupled with spectrum subtraction	-Regains the zero order spectra of the interfering substances -Applicability to partial and sever overlapped spectra	-Requires standard solutions of the interfering compound to be used as a divisor. -Requires tests to choose the best concentration for dividing
Mean centering	The transformed signals are evaluated at the highest peak point,	Coding of algorithms (special sequence in Matlab®)

Table 2 Advantages and disadvantages of ultraviolet spectrophotometric methods for the determination of the minor component presented in different fixed-dose pharmaceutical combinations (Continued)

Methods	Advantages	Disadvantages
	for optimum maximum sensitivity, levels De-noising and raising the signal to noise ratio	
Continuous wavelet transform		
	Many different wavelets family are often used for CWT analysis as they allow the separation of phase and amplitude components associated with the signal.	Several experiments were required to find the suitable wavelet family to complete the separation process successfully
Methods based on sample enrichment by sample spiking (standard addition) or spectrum addition technique		
Sample spiking (standard addition)	-Determines low concentration of minor component when eviating from Beer's law	Depending on one standard added for determination
Spectrum addition	-Determines low concentration of minor component when deviating from Beer's law -More accurate results comparing to sample spiking (standard addition)	-Depending on one standard spectrum for determination.

to the pharmaceutical preparation to achieve its linearity and then subtracting as mentioned in the first technique. These techniques are very helpful when the concentration of minor components is very low and deviated from its linearity [22].

The reported applications of the previously ultraviolet spectrophotometry methods are listed in Table 1. Also, the advantages and disadvantages of ultraviolet spectrophotometric methods for the determination of the minor components presented in different fixed-dose pharmaceutical combinations are listed in Table 2.

Conclusion

The most notable progress in the field of ultraviolet spectroscopy was experienced in the last two decades (2000–2020). The integration of the mathematical equations contributes to the discovery of new paths in the field of research for the application of UV spectroscopic methods in the determination of fixed-dose combination drugs with minor components.

Determining this mentioned drug combinations in pharmaceutical formulations with reasonable accuracy and precision has tested the applicability of the existing methods; thus, it may be excellent alternatives to other hyphenated analytical techniques.

Abbreviations

ANN: Artificial neural networks; USM: Ultraviolet spectrophotometric methods; PLS: Partial least-squares

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Authors' contributions

We have assured that "all authors have read and approved the manuscript." All the authors have equal contribution and participation in this research work. RO and DA designed the work; collected all the data, methods, and

theoretical background; and wrote the review. AS revised the "Methods" and "References" sections. HL supervised the review in all stages, revised the whole review, and updated it.

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Competing interests

The authors declare that they have no competing interests.

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