Open Access **Baghdad Science Journal** **P-ISSN: 2078-8665**
Published Online First: May 2022 **2022, 19(6): 1276-1285** **E-ISSN: 2411-7986**

DOI: https://dx.doi.org/10.21123/bsj.2022.6422

Simultaneous Ratio Derivative Spectrophotometric Determination of Paracetamol, Caffeine and Ibuprofen in Their Ternary Form

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Received 16/6/2021, Accepted 22/11/2021, Published Online First 20/5/2022, Published 1/12/2022

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Abstract:

A new, accurate, precise and economic two spectrophotometric methods for determination of Paracetamol (Par), Ibuprofen (Ibu), and Caffeine (Caf) were suggested. Those methods were the first and second ratio derivative spectrum using a double devisor. Par, Ibu, and Caf showed many useful peaks for their quantified determination. The validity of all analysis modes for determination of the three compounds, peak to baseline, peak area and peak to peak were according to ICH. The linearity of two methods was between 5 µg/ml as a lower concentration and 50 µg/ml as the highest concentration for three compounds. Recovery percentage was around 100% and relative standard deviation was less than 2.6%. The methods were applied successfully in the determination of Par, Ibu, and Caf in pure and pharmaceutical forms.

Keywords: Caffeine, Ibuprofen, Paracetamol, Peak area, Ratio derivative.

Introduction:

Paracetamol belongs to aromatic amides[1], (acetaminophen), it is used to relieve the pain [2], antipyretic and analgesic drug, [3] its molecular weight is 151.17 g.mol-1. Its structure is shown in Fig 1[4].

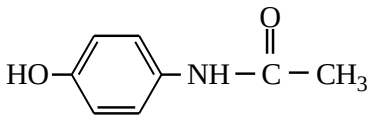

Figure 1. Structure of Paracetamol

Caffeine is 1, 3,7–trimethyl Xanthin-2,6-dihydroxy purine. It has the structure as in Fig 2 [4]

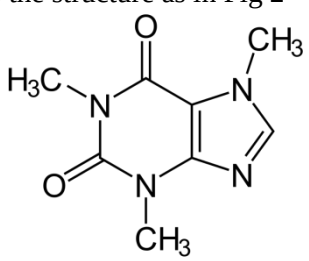

Figure 2. Structure of Caffeine

Caf is one of the families of xanthines. The xanthines that is concedered of plant origin may be the oldest stimulants. Caffeine is the strongest xanthine in its ability to increase alertness, postpone sleep[5].

Caf is a vasodilator (relaxes the blood vessels) as well as a diuretic (increases urination). Excessive consumption of caffeine can lead to negative effects on the organism, so it is recommended to reduce it. However, the effect of caffeine on cognition and memory requires further study [6].

Ibuprofene is chemically 2[4-(2-methyl propyl) phenyl] propanoic acid. The molecular weight is 206.28 and its structure is shown in Fig 3 [4].

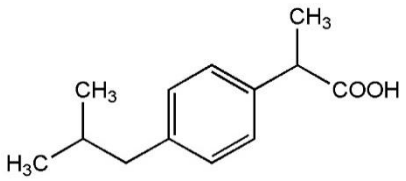

Figure 3. Structure of Ibuprofen

The relief of pain is not always easily achieved[7]. Opioid analgesics are effective but have

annoying consequences, may behave dangerous side-effects and their potential may lead to difficulties. Non-steroidal anti-inflammatory drugs have less regulatory limitations, but they also have vital negative effects that are likely to occur at a higher dose or with longer cycles[8]. Par is widely used and is highly safe at a dose of 4 g/day[9], but does not always supply enough pain relief on its own. Combining analgesics provides the potential of rising efficacy without rise the dose, which may cause risk[10]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often mixed with Par (prescribing of Par and Ibu together is known in medicine) mainly for postoperative pain drugs[11-13].

One study suggested that pre-emptive combination therapy including Par, Ibu, and Caf can be used efficiently to control postoperative pain after impacted third molar surgery[14]. Modern studies have shown that caffeine works as analgesic assistant when mixed with paracetamol[15].

A lot of different methods have been suggested for estimation of Par, Caf and Ibu simultaneously, such as first-order derivative spectroscopy[16,17], Zero- crossing derivative spectrophotometric method[18,19], Titrimetric-UV Spectrophotometric Method[20], Simultaneous spectrophotometric determination of Par, Ibu and Caf in pharmaceuticals by Chemometric methods[21,22], first-order derivative and wavelet transforms to UV spectra[23],first ratio derivative[24], first ratio derivative and H-Point[25] and visible method[26,27].

High Performance Liquid Chromatography methods (HPLC) [28-31], and different electrochemical methods either for each one alone or combined together[32-35]were used too in the estimation of the three compounds in the same form.

This study aims to develop a new simultaneous spectrophotometric method depending on the double devisor ratio derivative method.

Material and Methods:

Instrumentals and Chemicals

A computerized Shimadzu Spectrophotometer display 1650 Uv-vis double beam with 1 cm cells was used in the measurements.

All chemicals were analytical grade and had have high purity, so when used they did not need more purification. Standards Par, Ibu, and Caf were provided from the state company for drug industries and medical appliances (SDI) Samarra-Iraq. Stock solutions of Par, Ibu and Caf (1000 ppm) were prepared separately by dissolving 0.1g of each substance in an amount of distilled water and the volume was completed to the mark of 100 ml volumetric flasks with the same solvent (Ibu needed sonication for five minutes in an ultra-sound water bath to complete the solubility) and stored it in (individually not mixture) a dark place until use. Other dilutions were prepared as needed using distilled water. Tablets Dologan Denk (manufactured by Denk Pharma, Germany) labeled to contain 250, 200, and 50 mg/tablet of Par, Ibu, and Caf respectively, it were purchased from Iraqi local markets.

Procedure

Three groups of ternary mixtures solutions and three groups of binary mixtures solutions with different concentrations simulated the claimed ratio of three compounds in pharmaceutical forms were composed by preparing 5-50 µg/ml of Par, Ibu and Caf as mentioned in the preparation of standard solutions as in Table 1 and the required dilutions were conducted by using distilled water. The absorbance spectra of the three compounds were scanned between 200-400 nm and stored on a computer. The spectrum of the ternary mixture of each group was divided on the spectrum of the binary mixture (double divisor) of the same group in order to get the ratio spectrum of each compound separately.

Table1. The groups of ternary and binary mixtures of paracetamol, Ibuprofen and Caffeine

Group	Ternary mixtures µg/ml	Binary mixtures µg/ml
1	Par:Ibu:Caf 5-50:40:10	Ibu:Caf 40:10
2	Ibu:Par:Caf 5-50:50:10	Par:Caf 50:10
3	Caf:Par:Ibu 5-50:50:40	Par+Ibu 50:40

Analysis of Pharmaceutical Preparations

Twenty tablets of the pharmaceutical form (Dologan Denk) were weighed, powdered, and homogenized. An accurately weight of the mixture powder equivalent to 50:40:10 mg of Par:Ibu: Caf respectively, was dissolved in enough amount of distilled water, sonicated in an ultrasound water bath for five minutes, centrifuged at 3000RPM for 15 min, decanted the clear solution and the volume was completed to the mark by distilled water in 100 ml volumetric flask to get the concentration 500:400:100 µg/ml of Par:Ibu: Caf respectively.

Background of the Ratio Derivative Method

The ratio derivative method depends on the dividing of ternary mixture spectrum (the concentration of one compound is variant) by the binary mixture spectrum (fixed concentrations), the concentrations of the binary compounds may be

same in the pharmaceutical forms or not, according to the following equations:

$$Am,\lambda1 = \varepsilon x,\lambda1 * cx + \varepsilon y,\lambda1 * cy + \varepsilon z,\lambda1 * cz \quad --1$$

$Am,\lambda1 =$ absorbance of the ternary mixture at $\lambda1$

$\varepsilon x,\lambda1, \varepsilon y,\lambda1, \varepsilon z,\lambda1$ the absorptivity of x, y, z respectively.

In the same method the absorbance of the binary mixture of other compounds x, y (double divisor):

$$An,\lambda1 = \varepsilon x,\lambda1 * Cx + \varepsilon y,\lambda1 * Cy \quad -----\ 2$$

By dividing of equation1 on equation 2

$$\frac{Am,\lambda1}{An,\lambda1} = \frac{\varepsilon x,\lambda1*cx+\varepsilon y,\lambda1*cy+\varepsilon z,\lambda1*cz}{\varepsilon,\lambda1*cx+\varepsilon y,\lambda1*cy} \frac{\varepsilon x,\lambda1*cx+\varepsilon y,\lambda1*cy}{\varepsilon x,\lambda1*cx+\varepsilon y,\lambda1*cy} + \frac{\varepsilon z,\lambda1*cz}{\varepsilon x,\lambda1*cx+\varepsilon y,\lambda1*cy}$$

$$= k + \frac{\varepsilon z,\lambda1*cz}{\varepsilon x,\lambda1*cx+\varepsilon y,\lambda1*cy} ----- 3$$

If the concentrations of x and y were equal, K = 1, if they not equal, K doesn't equal 1.

When the equation 3 differentiated

$$\frac{d}{d\lambda}\left[\frac{Am,\lambda1}{An,\lambda1}\right] = \frac{d}{d\lambda}\left[\frac{\varepsilon z,\lambda1*cz}{\varepsilon x,\lambda1*cx+\varepsilon y,\lambda1*cy}\right] + \text{zero}$$

The derivative of instrumental response depends on the concentrations Cx, Cy, and Cz in the ternary mixtures but doesn't depend on the concentrations C'_{Par}, C'_{Caf}, and C'_{Ibu} in binary experimental mixtures.

Results and Discussion:

Different solvents were used to dissolve the three compounds such as ethanol, methanol and distilled water, or their mixtures with or without NaOH or HCl. Par and Caf were directly dissolved in distilled water while Ibu needed to be put in an ultrasound water bath for 5 minutes in order to complete the dissolution. The distilled water was used in the dissolution of the three compounds and in the next experiments.

The absorption spectra of Par, Ibu, and Caf under the Optimum conditions were scanned between 190-400 nm. The three compounds showed λmax at 242, 222, and 274 nm respectively as in Fig 4. The spectra of three compounds showed strong overly of their spectra. Therefore, the double divisor ratio derivative spectrophotometry was used for the simultaneous determination of three compounds.

Ratio Spectra Derivative Method

The ratio spectra of each of the three compounds are shown in Fig 5. The first and second derivative of ratio absorbance spectra of Par, Ibu, and Caf showed many positive and negative (valley) peaks at different wavelengths as in Figs 4-11. These peaks were very useful in the quantitative determination of these compounds either in pure or in pharmaceutical forms. The optimum conditions were used, Fast Scan Speed of the wavelengths = 2 and Sampling Interval = 2 nm which is the difference between the measurements, Delta lambda (Δλ) it is the minimum wavelength difference between two lines in a spectrum that can be distinguished, and Scaling Factor (S.F), it is a number which scales, or multiplies, some quantity. The values around 20-160 nm of Δλ were tested. It is noticed that when Δλ value was more than 20, the spectrum becomes distorted. The S.F values for 1st and 2nd ratio derivative were 2.35, 15 for Par, 20.6, 180 for Ibu and 52, 340 for Caf, respectively. These values gave high sensitivity of the method through the high values of the slopes of calibration curves and correlation coefficient (R). The concentration of three compounds in binary mixtures was chosen to simulate their concentrations in pharmaceutical forms as in Table 2.

Table 2. The values of optimum conditions according to the order of ratio derivative

Drug	Values of S.F		Δλ nm		Scan speed nm		Interval sample nm	
	1st order	2nd order	1st order	2nd order	1st order	2nd order	1st order	2nd order
PAR	2.35	15	20	20	fast	fast	2	2
IBU	20.6	180	20	20	fast	fast	2	2
CAF	52	340	20	20	fast	fast	2	2

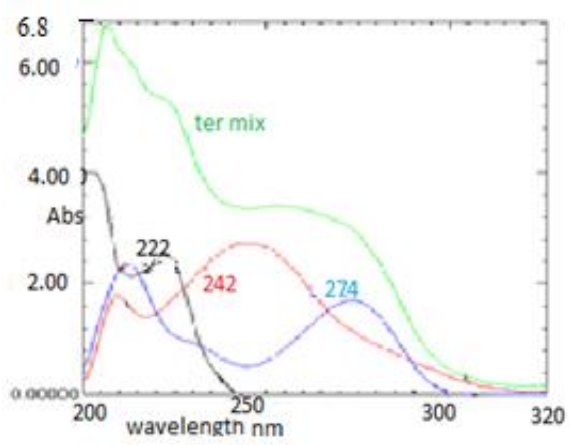

Figure 4. The U V-spectrum of Paracetamol (–), Caf (–) and Ibu (–)

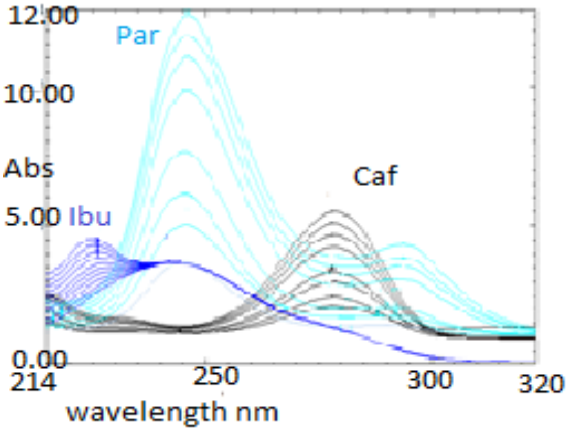

Figure 5. The ratio spectra of Paracetamol (–), Caffeine (–) and Ibuprofen (–)

Determination of Paracetamol

The first ratio derivatives of Par showed two peaks, at 234 and 258 nm as in Fig 6. The peak to the baseline of two peaks was proportional with the concentration of Par up to 10-50 µg/ml and 5-30 µg/ml respectively. The peak area between 216-246 and 248-282 nm was proportional to the concentrations of Par up to 10-40 µg/ml and 5-50 µg/ml respectively. While the second ratio derivative showed three peaks at 228, 246, and 266 nm as in Fig 7. The peak to baseline at 228 nm and it's area at 216-236 nm was proportional to the concentrations of Par up to 10-50 µg/ml. The peak to baseline at 246 nm and it's area at 236-256 nm was proportional to the concentrations of Par up to 5-25 and 30-50 µg/ml for the peak to baseline and 10-50 for to the peak area. The peak to the baseline at 266 nm was proportional with concentrations of Par up to 5-30 and 35-50 µg/ml, while the peak area at 256-286 nm was proportional with the concentration of Par up to 5-50 µg/ml. The peak to peak 246+266 nm was proportional to the concentration of Par up to 25-50 µg/ml.

For the first ratio derivative, the slopes of all calibration curves were between -0.1861–0.0602, R values were between 0.9986-0.9997, the limit of detection (LOD) and limit of quantification (LOQ) were between 0.1757-1.6302 µg/ml and 0.5271-1.6302 µg/ml respectively. While for the second ratio derivative, the slopes of all calibration curves were between -0.699-0.5634, R values were between 0.9946-0.9997, LOD, and LOQ were between 0.034-1.3526 and 0.1026-4.0587 µg/ml respectively. The results showed that the method has good linearity and good sensitivity.

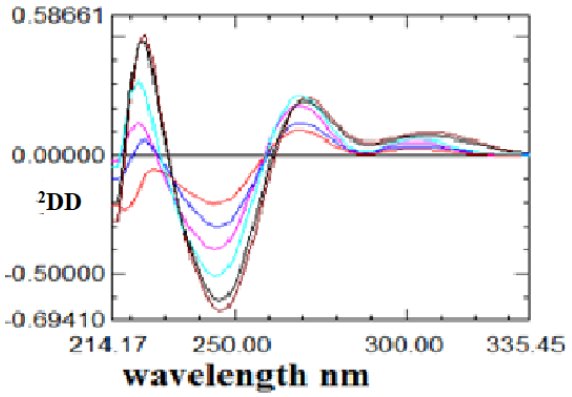

Figure 7. Second Ratio derivative of 5-50 µg/ml Paracetamol

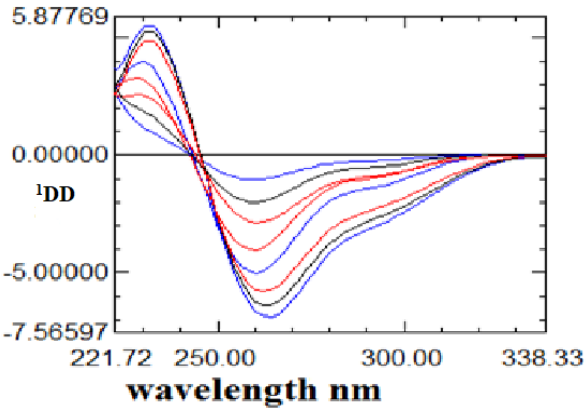

Figure 6. First ratio derivative of 5-50 µg/ml Paracetamol

Determination of Caffeine

The first ratio derivatives of Caf showed two peaks, at 264 nm and 292 nm as in Fig 8. The peak to baseline for two peaks and the peak area between 242-278 and 278-314 nm were proportional with the concentrations of caffeine up to 10-50 and 10-45 µg/ml and 10-35 µg/ml respectively. The second ratio derivative showed three peaks at 252, 280, and 300 nm as in Fig 9. The peak to baseline at 252 nm and it's area at 238-266 nm were proportional to the concentrations of Caf up to 5-50 µg/ml and10-50 µg/ml respectively. The peak to baseline at 280 nm and its area at 266-290 nm were proportional to the concentrations of Caf

up to 5-50 µg/ml. The peak to baseline at 300 nm was proportional to concentrations of Caf up to 5-50 µg/ml. The peak to peak either 252+280 or 280+300 nm was proportional with the concentration of the Caf up to 5-50 µg/ml.

For the first ratio derivative, the slopes of all calibration curves were between -0.9513-1.8973, R values were between 0.9986-0.9996, LOD, and LOQ were between 0.0529-0.0892 and 0.2676-0.1587 µg/ml respectively. While for the second ratio derivative, the slopes of all calibration curves were between -2.5404-1.2286, R values were between 0.9988- 0.9999, LOD, and LOQ were between 0.0683-0.0958 and 0.2044-0.2874 µg/ml respectively. The results showed that the method has good linearity and good sensitivity

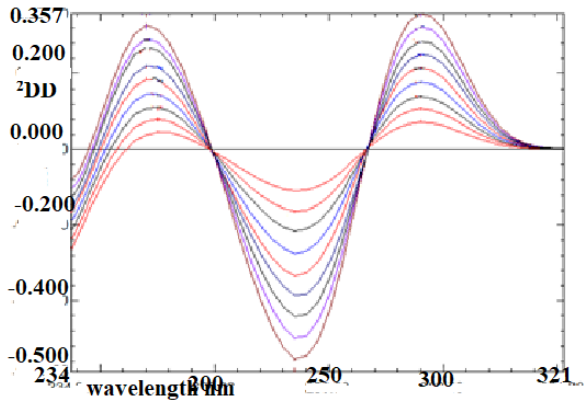

Figure 9.Second ratio derivative of 5-50 µg/ml Caffeine

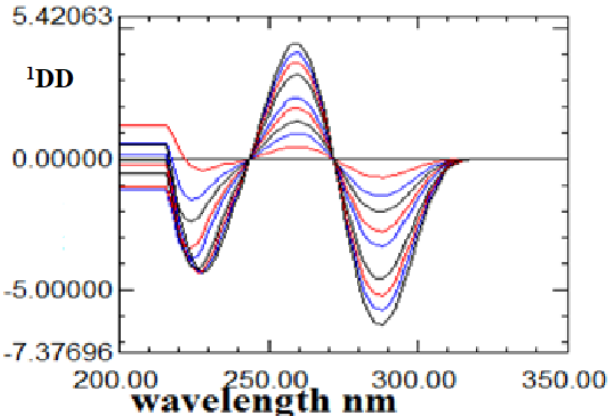

Figure 8. First ratio derivative of 5-50 µg/ml Caffeine

Determination of Ibuprofen

The first ratio derivatives of Ibu showed one useful peak at 234 nm as in Fig10. This peak and its area between 234-252 nm were proportional with the concentrations of Ibu up to 5-50 and 5-45µg/ml respectively. The second ratio derivative showed two peaks at 224 and 238 nm as in Fig11. The peak to baseline at 224 nm and it's area at 222-232 nm were proportional to the concentrations of Ibu up to 10-45 and 30-50 µg/ml respectively. The peak to baseline at 238 nm and its area at 232-256 nm was proportional to the concentrations of Ibu up to 10-45 and 5-50 µg/ml respectively.

For the first ratio derivative, the slopes of all calibration curves were between -0.2562 to -0.0362, R values were between 0.9995-0.9999, LOD, and LOQ were between 0.0638-0.0827 nd 0.1914-0.2481 µg/ml respectively. While for the second ratio derivative, the slopes of all calibration curves were between -0.3116-0.4157, R values were between 0.9966-0.9999, LOD, and LOQ were between 0.0152-1.5620 and 0.0465-4.6860 µg/ml respectively. The results showed that the method has good linearity and good sensitivity.

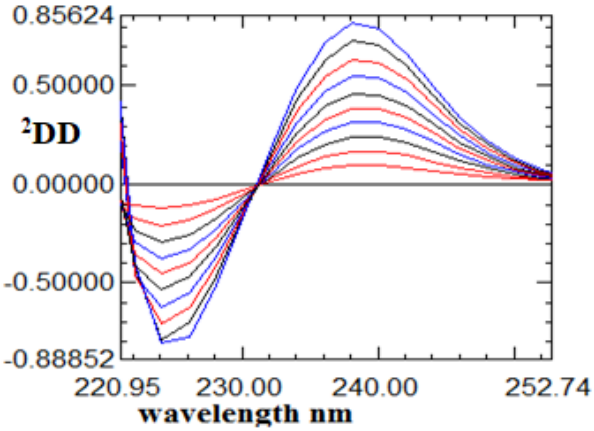

Figure 11. Second ratio derivative of 5-50 µg/ml Ibuprofen

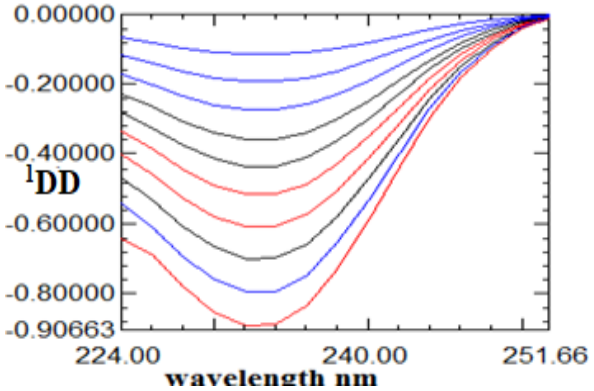

Figure 10. First ratio derivative of 5-50 µg/ml Ibuprofen

Validation of the Methods

The procedures were carried out according to the International Conference on Harmonization. The method was validated for selectivity, linearity, accuracy, sensitivity, precision.

Selectivity

Selectivity is the possibility of the method to differentiate between the analyte and other compounds in the sample under analysis. The method was selective to the determination of Par, Caf, and Ibu in the same sample without any

interference, this result can be noted by the analysis of each compound with another two compounds which was very close and have recovery percentage values around 100%.

Linearity

The linearity was described by plotting the linear regression of the taken concentrations using ten concentrations against the response of the apparatus. The linearity was not less than 5 µg/ml and not more than 50 µg/ml for all calibration curves of three compounds as in Table 3.

Accuracy and Precision

The accuracy and precision for all calibration curves were tested. They were conducted of seven replicate measurements.

Accuracy means, the closeness of the true value of the concentration of the analyte and the mean of the measurements of the analytical procedure. While the precision means the convergence of measured values with each other. The precision is performed in the same day (within batch intra-day), and in more than one day (between batch inter-day). Accuracy is the term that expresses for recovery percentage Rec%, the precision expresses for relative standard deviation RSD%.

The results showed the accuracy for all measurements agreed and ranged around 100% and the precision was less than 2.6% for the determination methods of Par, Caf, and Ibu either within a day or between day as in Table 3.

Table 3. Accuracy and Precision of Paracetamol, Caffeine and Ibuprofen

Compound	Order of derivative	Mode of analysis	λ nm	Linearity µg/ml	RSD%		Rec%
					intra-day	**inter-day**	
Par	^{1}DD	Peak to base line	234	10-50	0.21905-0.92847	0.07635-0.55928	96.14618-102.75138
			258	5-30	0.94717-0.99028	0.03093- 0.73052	98.41109-104.00000
		Peak area	216-246	10-40	0.59257-1.5718**9**	0.85171-1.77305	96.16095-103.52066
			246-282	5-50	0.82902-1.05289	0.57290-2.04814	95.51252-103.06983
	^{2}DD	Peak to base line	228	10-50	0.37183-0.93817	1.10421-2.57025	97.29182-101.49077
			246	5-25	0.62541-1.02859	0.83949-1.55610	98.02278-102.30633
				30-50	0.16496-0.71258	0.89745-1.99025	98.07020-102.88847
			266	5-30	1.01853-1.40018	0.09158-1.18480	98.00895-104.40268
				35-50	0.74946-1.28179	0.95301–1.83095	97.38192-103.08844
		Peak area	216-236	10-50	1.52856-2.34190	0.58326-1.63013	95.18412-102.19474
			236-256	10-50	0.37191-1.83018	0.99422-1.96205	95.43883-102.84265
			256-286	5-50	0.67154-1.84939	0.71256-2.19468	96.04651-103.14730
		Peak to peak	246+266	25-50	0.88613-1.77473	0.09573-1.85294	96.15800-103.85307
Caf	^{1}DD	Peak to base line	264	10-50	0.36717-	0.07105-1.49283	95.24601-100.92923
			292	10-45	1.875450.53610-0.92019	0.42832-1.95038	95.73275-102.66447
		Peak area	242-278	10-35	0.65824-1.43959	0.73846-0.99655	96.78139-103.14338
			278-314	10-35	0.46216-0.99017	0.42015-1.66983	96.31470-103.05551
	^{2}DD	Peak to base line	252	5-50	0.45352-1.00687	0.18345-0.94729	97.03471-102.64969
			280	5-50	0.54216-0.89527	0.82764-1.12482	98.78576-101.12202
			300	5-50	0.69258-1.18753	0.84926-1.27317	99.38664-102.60095
		Peak area	238-266	10-50	0.82949-0.91106	1.00472-1.41059	95.02972-103.17728
			266-290	5-50	0.68241-0.88763	0.72011-1.20480	95.64471-102.62005
		Peak to peak	252+280	5-50	0.91804-1.91728	0.07941-1.14591	96.27371-102.74916
			280+300	5-50	0.85481-1.00035	0.28401-0.95713	95.31184-102.74918
Ibu	^{1}DD	Peak to base line	234	5-50	0.15983-1.08256	0.28175-1.22985	97.17508-104.61603
		Peak area	224-252	5-45	0.35710-1.53183	0.58388-1.63035	97.84661-101.48717
	^{2}DD	Peak to base line	224	10-45	0.96713-1.42204	0.39438-0.94862	99.22414-101.17446
			238	10-45	0.17382-0.61156	0.29568-0.89326	96.95693-102.98037
		Peak area	222-232	30-50	0.43097-0.80122	0.58209-1.04862	96.95695-102.36243
			232-256	5-50	0.13572-0.52686	0.03882-0.18574	97.00023-101.53376

Limit of Detection and Limit of Quantification

The limit of detection (LOD) is the smallest concentration of analyte in the test sample that can be reliably distinguished from zero. The limit of quantification (LOQ) is the smallest concentration of a material that can be quantitatively measured. The LOD and LOQ for all methods of determination of three compounds refer to good

sensitivity, their values ranged between 0.1520-1.56200 and 0.4560-4.68600 µg/ml depending on the lowest concentration on the calibration curves for the three compounds.

Methods Application

The application of the suggested methods is achieved by using the regression equations of the calibration curves of all analysis modes of three compounds. Two concentrations for each compound were chosen for the application. They are 25 and 50 for Par, 5 and 10 for Caf, and 20 and 40 µg/ml Ibu. All the results were in the acceptable ranges. Rec% values were around 100% and RSD% values were less than 2% either within a day or between days for three compounds as in Table 4.

Table 4. The Application of the Methods T-test

compound	Order of derivative	Mode of analysis	λ nm	Concentration µg/ml		RSD%		Rec%
				taken	**found**	**intra-day**	**inter-day**	
Par	^{1}DD	Peak to base line	234	50	50.10481	0. 3937	0. 83351	100.20962
				25	26.00000	1.39582	1.14960	104.00000
			258	25	25.59321	1.27390	1.15832	102.37285
		Peak area	216-246	25	25.52950	0.92595	1.29584	102.11800
			246-282	50	49.39584	1.50139	1.59483	98.79168
				25	25.24818	1.52813	1.73920	100.99271
	^{2}DD	Peak to base line	228	50	49.49493	0. 72657	0.94837	98.98986
				25	25.59375	0.94817	1.28473	102.37500
			246	50	48.10935	10.84938	11.04867	96.21870
				25	25.16552	1.37610	1.64592	100.66209
			266	50	51.37488	1.27745	0.98150	102.74976
				25	25.74743	1.84729	1.95949	102.98974
		Peak area	216-236	50	47.85391	1.48295	1.38572	95.70782
				25	24.59820	1.47291	1.27485	98.39281
			236-256	50	24.99036	1.88251	1.63927	99.96144
				25	25.34567	1.03820	1.19472	101.38268
			256-286	50	51.52758	0.89482	1.24839	103.05516
				25	25.96180	1.27482	1.88372	103.84721
		Peak to peak	246+266	25	25.55486	1.07483	0.95856	102.21944
				50	51.69255	1.48205	1.33961	103.38510
Caf	^{1}DD	Peak to base line	264	10	10.47563	1.78392	1.84726	104.75630
			292	10	9.63958	1.74034	0.94836	96.39580
		Peak area	242-278	10	10.29473	1.85943	1.68946	102.94730
			278-314	10	9.90284	0.89402	0.79375	99.02840
	^{2}DD	Peak to base line	252	10	10.14957	1.09053	0.758392	101.49570
				5	4.97464	0.99471	1.33749	99.49282
			280	10	9.89476	0.78546	1.19486	98.94760
				5	5.08336	0.91620	1.22701	101.66725
			300	10	10.21950	1. 81753	1.52857	102.19504
				5	4.86353	0.88491	1.03827	97.27053
		Peak area	238-266	10	9.95748	1.90305	1.49683	99.57480
			266-290	10	10.16583	0.94726	1.40385	101.65830
				5	5.20009	1.52058	1.33951	104.00175
		Peak to peak	252+280	10	9.961847	0.80284	0.91148	99.61847
				5	4.82864	1.38104	1.19482	96.57285
			280+300	10	10.24958	1.40385	1.55730	102.49580
				5	4.79691	1.33950	1.13951	95.93827
Ibu	^{1}DD	Peak to base line	234	40	41.01092	1.17593	0.98985	102.52730
				20	20.73790	1.48821	1.19403	103.68950
		Peak area	224-252	40	39.59039	1.49783	0.86937	98.97598
				20	20.33009	1.35357	1.06503	101.65047
	^{2}DD	Peak to base line	224	40	40.49285	0.99836	1.29476	101.23213
				20	19.94090	1.18490	1.84593	99.70453
			238	40	41.03857	1.33968	0.88743	102.59643
				20	20.01168	1.59451	0.96720	100.05839
		Peak area	222-232	40	40.08593	1.85857	1.74659	100.21483
			232-256	40	39.69386	1.15473	1.08573	99.23465
				20	19.54980	0.96821	1.30651	97.74902

T-test

The t-test values for all measurements at 95% confidence were less than t table value (1.943), so the error was not systematical and the results are acceptable.

Conclusion:

New two methods for simultaneous determination of Par, Caf, and Ibu in Pharmaceutical forms were developed based on the double divisor first and second ratio derivative method. The results showed that these methods were precise, accurate, chief, simple, and can be applied in the daily determination of the mention compounds.

Authors' declaration:

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are mine ours. Besides, the Figures and images, which are not mine ours, have been given the permission for re-publication attached with the manuscript.
- Ethical Clearance: The project was approved by the local ethical committee in University of Samarra.

Authors' contributions statement:

S. T. A.: Suggestion of the proposal projet. K. A.: Complete the practical part, write the research, revision the corrections.

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Open Access **Baghdad Science Journal** **P-ISSN: 2078-8665**
Published Online First: May 2022 **2022, 19(6): 1276-1285** **E-ISSN: 2411-7986**

التقدير الطيفي الاني باستخدام المشتقة النسبية للباراسيتامول والكافايين والايبوبروفين في اشكالها ثلاثية المكونات

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الخلاصة:

تم اقتراح طريقتين جديدتين و دقيقتين و متوافقتين و اقتصاديتين للتقدير الطيفي لكل من الباراسيتامول و الايبوبروفين و الكافايين. والطريقتان هما المشتقة النسبية الاولى و الثانية ثنائية المقسوم عليه. و قد اعطى كل من الباراسيتامول و الايبوبروفين و الكافايين قمم مفيدة في التقدير الكمي لكل منهما. و قد تم تقييم جميع انواع تقنيات التقدير للمكونات الثلاثة و هي ارتفاع القمة الى خط الاساس ومساحة القمة و قمة الى قمة بالاستناد الى ICH. كان التناسب خطيا لكلا الطريقتين ما بين 5 مكغم/مل كاقل تركيز و 50 مكغم/مل كأعلى تركيز للمكونات الثلاثة. كانت الاسترجاعية المئوية حوالي 100% و الانحراف المعياري النسبي كان اقل من 2.6%. طبقت الطريقة بنجاح في تقدير كل من الباراسيتامول و الايبوبروفين و الكافايين في مكوناتها الصيدلانية.

الكلمات المفتاحية: الكافايين, الايبوبروفين, الباراسيتامول, مساحة القمة, المشتقة النسبية.