Journal of Pharmaceutical Research International

25(2): 1-14, 2018; Article no.JPRI.46503
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

First- order Derivative and UV-spectrophotometric Methods for Simultaneous Determination of Paracetamol, Ibuprofen, and Caffeine in Bulk and Parmaceutical Formulatation

Sura L. Alkhafaji[1*] and Abdulbari M. Mahood[1]

[1]Department of Pharmaceutical Chemistry, College of Pharmacy, University of Kerbala, Hai Almuadhafeen Campus, 1125, Karbala, Iraq.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI:10.9734/JPRI/2018/46503
Editor(s):
(1) Dr. R. Deveswaran, Associate Professor& Head, Drug Design and Development Centre, Faculty of Pharmacy, M.S.Ramaiah University of Applied Sciences, India.
Reviewers:
(1) Samuel M. Adadey, University of Ghana, Ghana.
(2) P. Rajakani, V. O. Chidambaram College, Manonmanium Sundaranar University, India.
(3) Victor Moses, Ahmadu Bello University, Nigeria.
Complete Peer review History: http://www.sdiarticle3.com/review-history/46503

Original Research Article

Received 12 November 2018
Accepted 28 January 2019
Published 04 February 2019

ABSTRACT

Aims: This work is to develop accurate and simple spectrophotometric methods with the first derivative for estimation of Ibuprofen (IBU), Caffeine (CAF) and Paracetamol (PAR) in bulk and pharmaceutical preparation.
Method: The methods use ethanol 90%: 0.1 N sodium hydroxide (25:75) as a solvent for analysis. The wavelengths were determined for each drug in the range of 200-400 nm in spectrum mode. UV-spectrophotometer-equipment used to calculate the first derivatives through which IBU, CAF, and PAR were evaluated for simultaneous assay. The validity of the methods is established on the basis of linearity, accuracy and precision, limit of detection and limit of quantification. The methods applied to estimate the level of PAR, IBU, and CAF in a capsule dosage form.
Results: The linearity of the methods was in the range of (1 - 15) µg /ml at λ max 220 nm for IBU, for CAF was (1-10) µg /ml at λ max 272 nm, and for PAR was (1-16.5) µg /ml at λ max 257 nm. In the second method, by application of first derivatives, IBU has an absorbance at 212 NM (in

**Corresponding author: E-mail: sura.l@uokerbala.edu.iq;*

contrast CAF and PAR have zero value at is this wavelength) whereas, CAF absorbed at 272 nm (in contract IBU and PAR have zero value at this wavelength) whereas PAR has absorbance at 230 nm (in contrast IBU and CAF has zero value). Upon derivative assay, the amount was 98.58 %, 98.15% and 98.66% for PAR, IBU, and CAF, respectively.

Conclusion: The suggested methods can be effectively applied for simultaneous determination of IBU, CAF and PAR in the bulk and capsule dosage form with good precision, recovery and less percentage of error.

Keywords: Ibuprofen; paracetamol; caffeine; first order derivative; UV- spectrophotometry.

1. INTRODUCTION

Ibuprofen (IBU) is (RS) – 2-(4-(2 methyl propyl) phenyl) propanoic acid [1] (Fig.1), non-steroidal anti-inflammatory drug (NSAIDs). It acts by inhibition of cyclooxygenase 2 (COX-2); therefore, It is recommended in many conditions such as controlling of mild to moderate pain and inflammation as in dysmenorrhoea, migraine, dental pain, postoperative pain, muscle and joint syndrome [2].

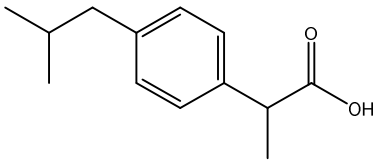

Fig. 1. Chemical structure of Ibuprofen (IBU)

Paracetamol or Acetaminophen (PAR), is an N-(4-hydroxyphenyl) acetamide (Fig. 2). It is classified as a non- steroidal anti-inflammatory drug as a result of its inhibition of prostaglandin production [3]. It has analgesic and antipyretic activity. It is frequently presented in combination with other drugs, for example, in cough medications [4]. In opioid analgesic medication [5,6]. PAR is typically given orally or rectally, but is also accessible intravenously.

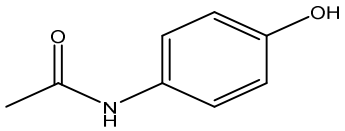

Fig. 2. Chemical structure of paracetamol (PAR)

Caffeine (CAF) is a trimethylxanthine derivative (Fig. 3). It is naturally standing up from several plants, including coffee beans, cocoa beans, and tea. CAF is considered as a central nervous stimulant that produces a state of wakefulness and raises the mental activity [7]. It also increases the incidence and depth of respiration by stimulation of the respiratory center [8]. These three ingredients (PAR, IBU and CAF) have been introduced in combination dosage form to meliorate the analgesic activity [9] or used separately with other pharmaceutical components.

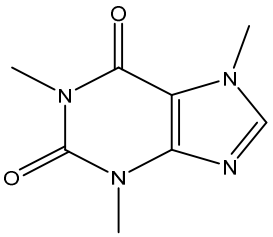

Fig. 3. Chemical structure of Caffeine (CAF)

Numerous analytical methods have been described for estimation of IBU, PAR, and CAF alone or in combination with other active ingredient, such as HPLC [10-22], electrochemical method [23-27], volumetry [28], GC-MS [29-31], UV - visible spectrophotometric analytical methods [32-37]. In recent times, the determination of binary or ternary mixture that has been accomplished by derivative spectrophotometry was lunched to be a useful method in determination of drugs without the interference effect of the formulation matrix by employing the zero- crossing method [38-40].

So, the aim of this work is to develop a reliable, precise, simple, linear, accurate, sensitive and effective method for simultaneous determination of Ibuprofen, Caffeine and Paracetamol in the ternary mixture and multi-component dosage form.

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

2.1.1 Pure drugs

Active therapeutic ingredients of PAR (purity 99.5%), IBU (purity 99.5%), CAF (purity 99.5%)

were kindly offered by Sammara drug industries SDI, Sammara, Iraq.

2.1.2 The solvents

Ethanol solvent 90% and sodium hydroxide NaOH 100% were supplied by HIMEDIA, India. Ethanol 90 % and 0.1 M NaOH (25:75) was selected as a solvent after several experiments for developing and improving the spectral characteristics of drugs. Distilled water was prepared in laboratories of the faculty of pharmacy.

2.1.3 NO pain® capsules

NO Pain® Capsules is a potent and long-acting combination medicine used in conditions such as osteoarthritis and dysmenorrhea to relieve pain. It may also be used to provide relief from mild to moderate pain associated with a headache, muscle sprains, joint pain, and dental pain. Pharmaceutical dosage form NO Pain® Capsules (Vitane Pharmaceuticals, Inc) containing paracetamol 325 mg, Ibuprofen 200 mg, and caffeine 30 mg was obtained from the local market.

2.2 Instrumentations

SHIMADZU- 1800 UV-visible spectrophotometry (Kyoto, Japan) equipped with a 1.0 cm quartz cell, supported by UV Probe 2.32 software has been used for spectrophotometric measurements. Analytical balance for weightings (Germany).

2.3 Preparation of Standard Stock Solution

A standard stock solution of (100 µg/ml) for each pure PAR, IBU, and CAF were prepared separately by accurately weighing about 10.10 mg of each drug, then dissolving in 25 ml of 95% Ethanol solvent, transferring into 100 ml volumetric flask and diluting to the mark with the 0.1 M NaOH. These solutions were employed as working standard stock solutions used for further study.

2.4 Preparation of Sodium Hydroxide Solution (0.1 M)

A solution of 0.1 M NaOH was prepared by dissolving 2.0 g in 500 ml volumetric flask with distilled water.

2.5 Preparation of the Powder Mixture

Starting from the previous standard stock solutions (100 µg/ml), standard solutions containing (10 µg/ml, 1.5 µg/ml and 16.5 µg/ml) were prepared in 50 ml volumetric flask by diluting three volumes (5 ml , 0.75 ml, and 8.25 ml) of IBU, CAF, and PAR, respectively. Then, these solutions made up to the mark with the solvent (25 ml of 95 % Ethanol and 75ml of 0.1 M NaOH). These diluted solutions were employed for further analysis.

2.6 Procedure for Pharmaceutical Preparation and spectroscopic Analyses

Ten commercial capsules (No Pain capsules), containing IBU 200 mg, CAF and PAR 325 mg, 30 mg, were weighted and grounded well to produce a powder. An accurately weighed amount of this powder equivalent to, 1.0 mg of IBU and 0.15 mg of CAF, 1.625 mg of PAR dissolved in solvent (25 ml of 95 % Ethanol and 75 ml of 0.1 M NaOH), mixed well and transfer to 100 ml volumetric flask and complete to the mark with the same solvent. the resulting solution was filtered using Whatman filter paper No. 41, to eliminate any insoluble material, then, the filtrate was transmitted to 100 ml volumetric flask and the solution made up to the mark with the previous solvent. The sample solution of the final concentration of 10.0 µg/ml of IBU, 1.5 µg/ml of CAF and 16.5 µg/ml of PAR was scanned between 200 nm and 400 nm against a reagent blank (25 ml of 95% Ethanol and 75 ml of 0.1M NaOH). The first derivative spectrum was recorded and the absorbance was measured at 212 nm, 230 nm, 272 nm for IBU, CAF, and PAR, respectively. The concentration of each analyte was determined by the equations generated from the calibration curves of corresponding drugs.

3. RESULTS AND DISCUSSION

3.1 Selection of Analytical Wavelength

Via suitable dilutions of the working standard stock solution, 10µg/ml of each drug were prepared and scanned separately in the wavelength region of 200- 400 nm versus the reagent blank. It was found that the λ max was 220 nm, 272 nm and 257 nm for IBU, CAF, and PAR, respectively.

The absorption spectrum adapted to first -order derivative using the spectrum mode at (200-400 nm) and it was observed that IBU was absorbed at 212 nm whereas PAR and CAF show absorbance at 230 nm and 272 nm, respectively. The absorbance of PAR and CAF was zero at wavelength 212 nm. Thus, 230 nm and 272 nm were selected as working wavelengths for PAR and CAF and for IBU, working wavelength selected was 212 nm for first derivative spectroscopy. The results are shown in (Figs. 4-11).

3.2 Calibration Graph

The linearity was obtained by diluting an accurate volume of stock solution (100 µg/ml) of each drug to make a different concentration set of IBU (1-15 µg/ml), CAF (1-10 µg/ml) and PAR (1-16.5 µg/ml). The absorbance was measured at a range of 200-400 nm, and the first derivative of the spectrum was taken. The derivative was measured for each of these solutions at the working wavelength and plotted against concentration to obtain the calibration curve as shown in (Figs. 12, 13, 14, 15, 16).

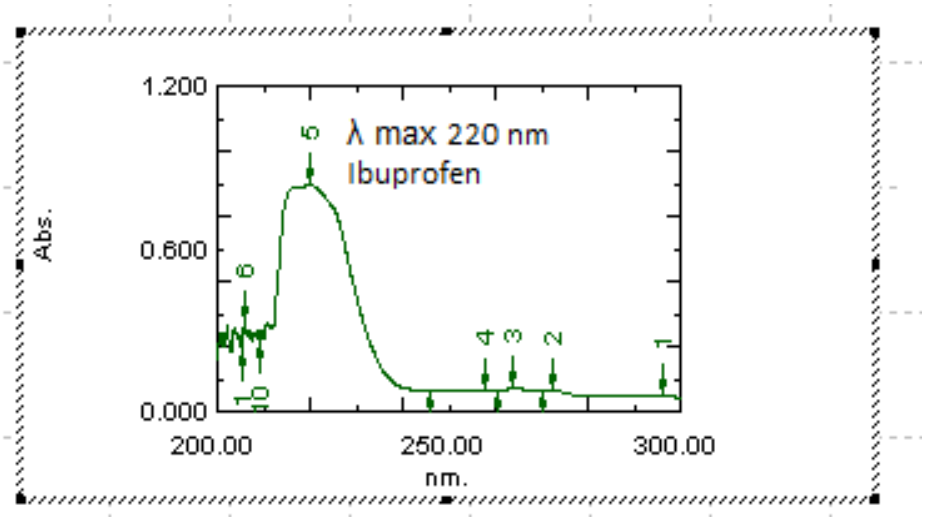

Fig. 4. UV absorption spectra of series of IBU at λmax= 224 nm

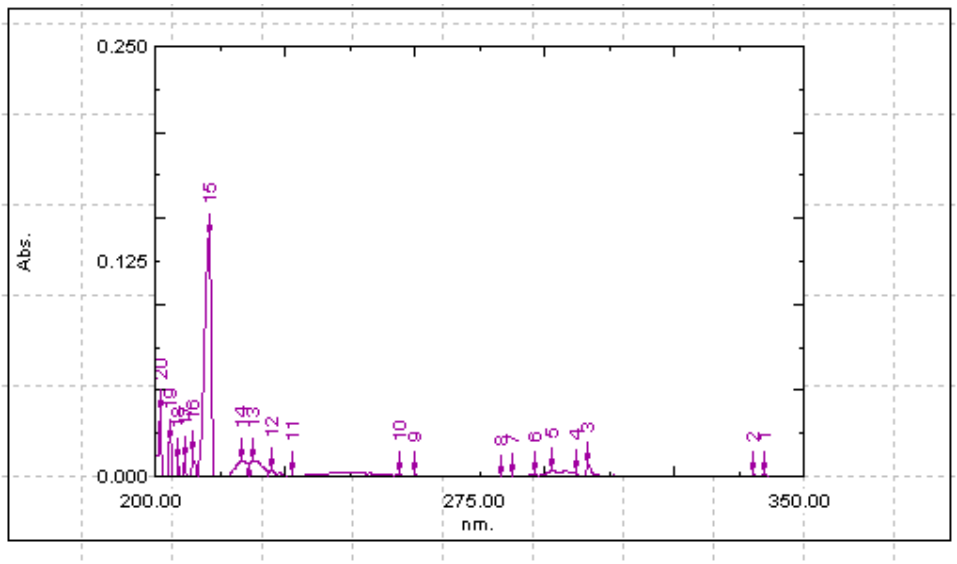

Fig. 5. First order derivative absorption spectra of IBU at λ max= 212 nm

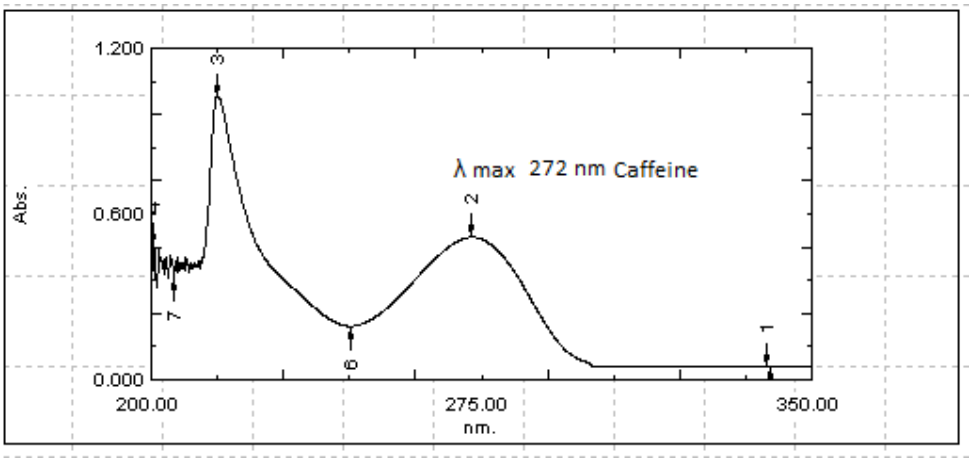

Fig. 6. UV absorption spectra of CAF at λmax= 272 nm

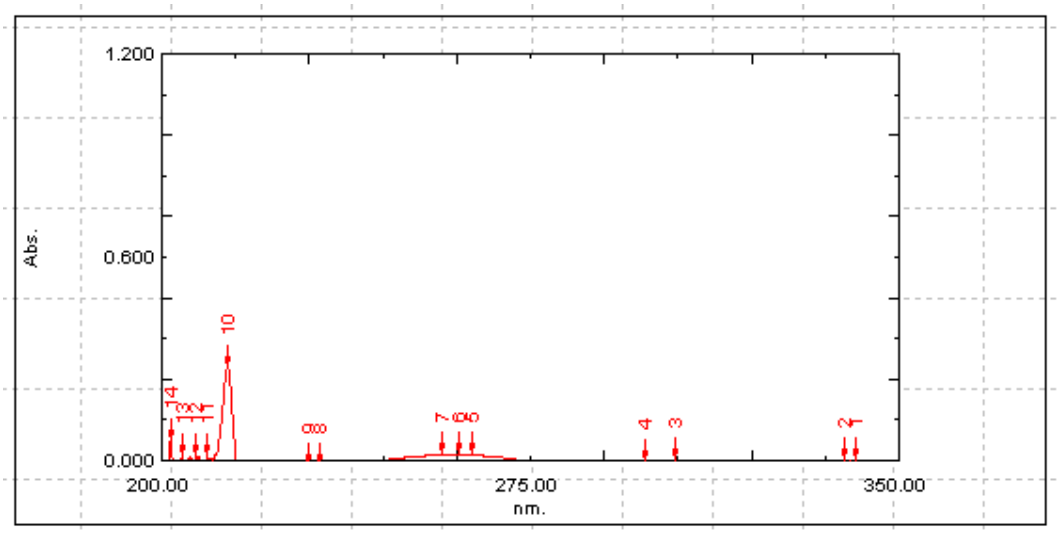

Fig. 7. First order derivative absorption spectra of CAF at λmax= 272 nm

3.3 The Validation of the Methods

Method validation parameter's like linearity, accuracy, precision, limit of detection and limit of quantification were accomplished for pure powder mixture and capsule dosage form.

3.3.1 Linearity

The linearity of the anticipated methods was estimated by regression analysis of the calibration graphs. The results acquired from zero and first-order derivative explain that the methods applied were linear within concentrations range in construction of the calibration curve, with their regression coefficient (r^2) all nearly to one. Based on the standard deviation SD and the slop of the calibration curve, Limit of quantification LOQ and limit of detection LOD were calculated. The results are listed in Table 1.

3.3.2 Accuracy and precision

The accuracy of these proposed methods was estimated by recovery studies. The accuracy of the analytical method was measured for a series of seven replicates of three levels of concentration PAR, CAF, and IBU. The recovery percentage (98-99.6 %) and (98-100%) for the first method and second method, respectively indicate that these methods are accurate with an acceptable error. The precision was signified by the percent relative standard deviation RSD %.

The RSD % calculated is less than 2 which show that the methods used are highly precise for estimation of these ingredients in pure form and in the pure mixture. The results are summarized in Tables 2, 3, 4 and 5.

3.3.3 Limit of detection and limit of quantitation

On the basis of standard deviation, intercept and slope, limit of detection LOD and Limit of quantitation LOQ were estimated using formula LOQ= 10 σ /S and LOD= 3.3 σ/S, where, σ is the standard deviation of the response and S is the slope of the calibration curve of a sample. Analysis of the LOQ and LOD values which are shown in Table 1 for the proposed methods was indicated a good precision.

3.4 Application

The accuracy of the formulated product was confirmed by recovery studies from capsules at different concentration levels. The mean percentage recoveries were found (98.00-100 %) as shown in Table 6. The results for this assay were reproducible when verified by standard method stated in British Pharmacopeia (2006) as shown in Table 7.

3.4.1 Analysis of (No Pain) ® capsule formulation

A sample solution of final concentration containing 10.0 µg /ml of IBU, 1.5 µg/ml of CAF and 16.25 µg/ml of PAR, were analysed using suggested methods and the absorbance was measured at 230 nm, 212 nm and 272 nm for PAR, IBU, and CAF, respectively (Fig.17 and Fig.18). The concentrations of PAR, IBU and CAF were estimated using calibration curve. The results are shown in Table 7.

3.4.2 Evaluation of the results of proposed methods

The efficiency and success of the proposed methods were tested and compared to results of standard method were used in British pharmacopoeia (2006). The reliability of the proposed methods was estimated by applying specific statistical tests (t-test) and (F-test). The results of (t –test) and (F-test) as summarised in Table 8, indicated that there is no significant difference between the accuracy of suggested methods and the standard method used for estimation of marketed dosage form.

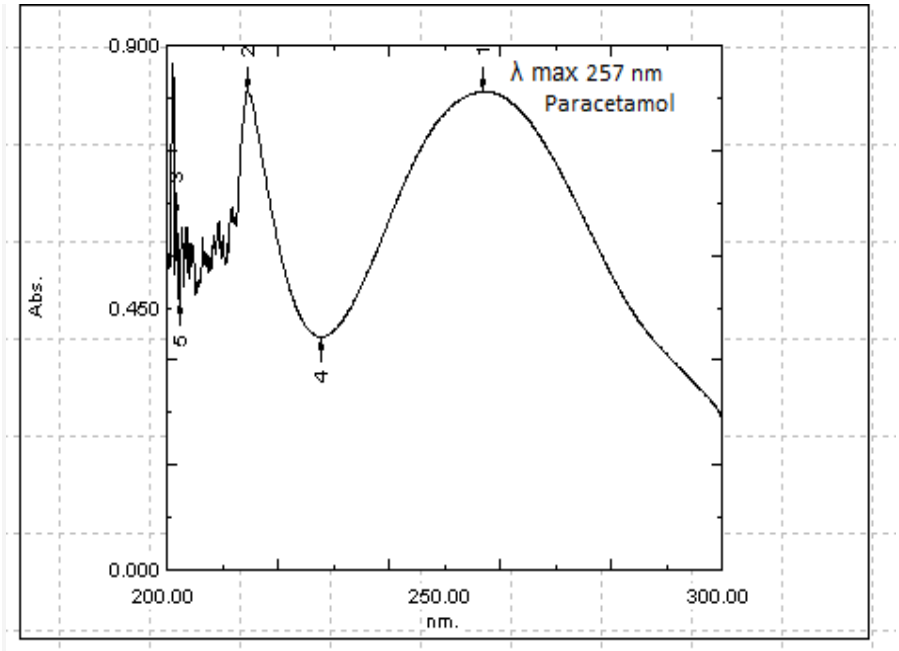

Fig. 8. UV absorption spectra of PAR at λmax= 257 nm

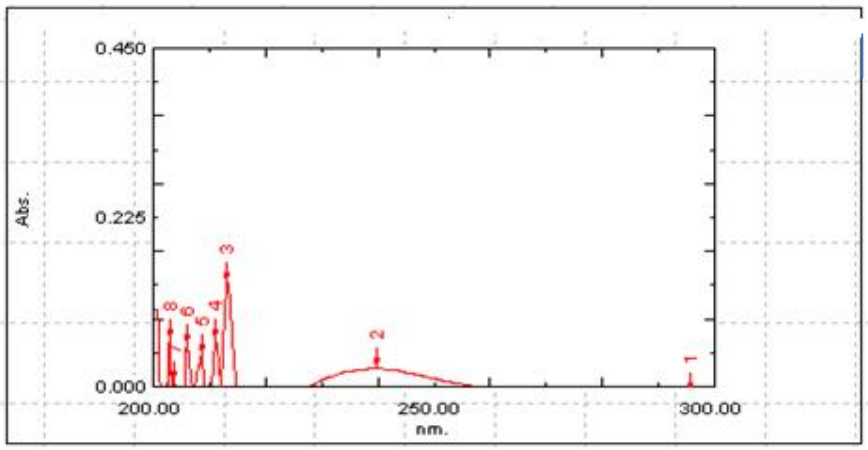

Fig. 9. First order derivative absorption spectra of PAR at λmax= 230 nm

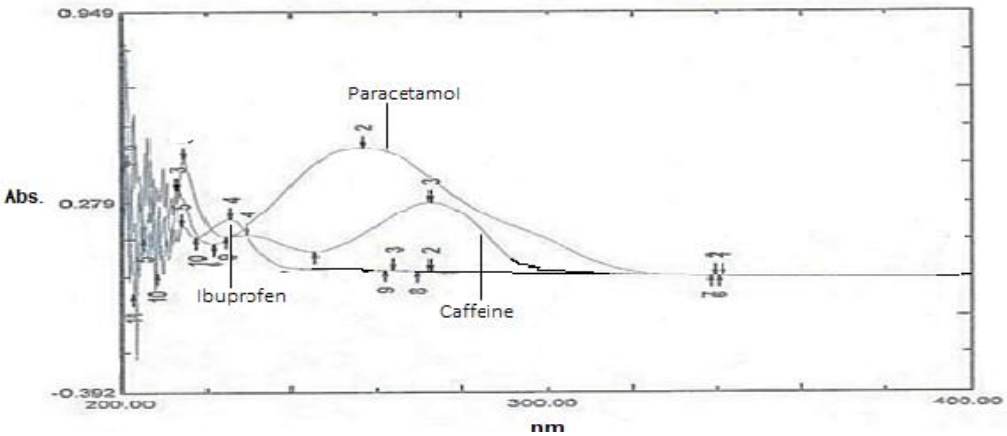

Fig. 10. The overlay UV spectrum 10.0 µg/ml IBU, 1.5 µg/ml CAF and 16.5 µg/ml PAR

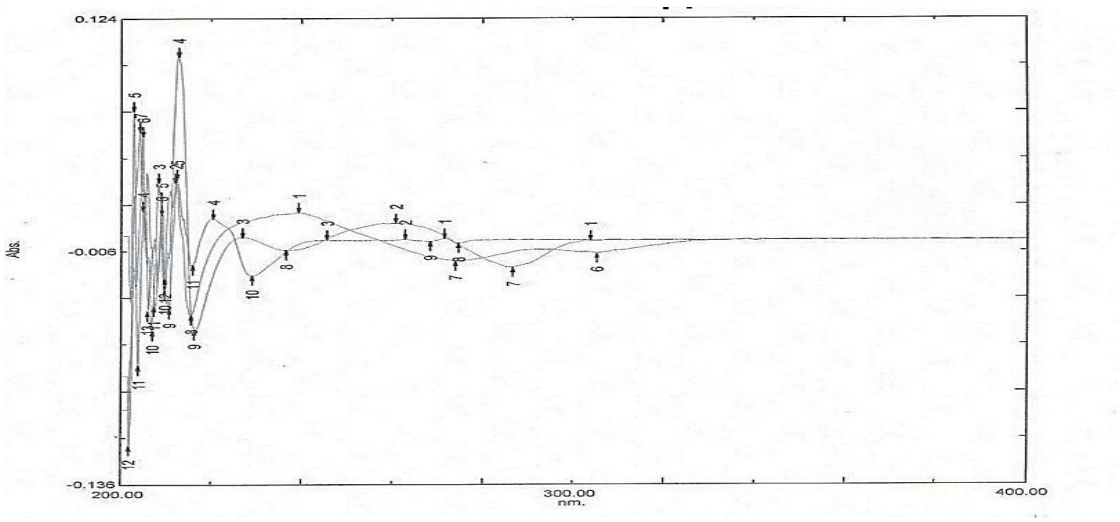

Fig. 11. First order derivative overly of UV spectra of 10.0 µg/ml IBU, 1.5 µg/ml CAF and 16.5 µg/ml PAR

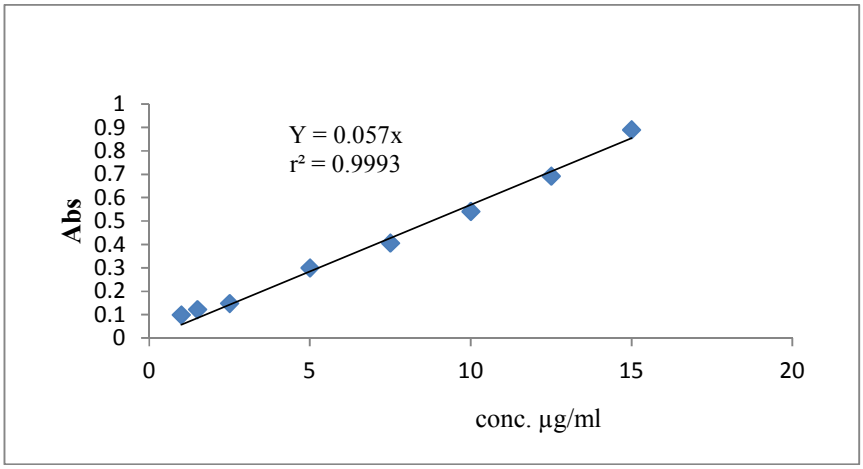

Fig. 12. Calibration curve of IBU at 224 nm

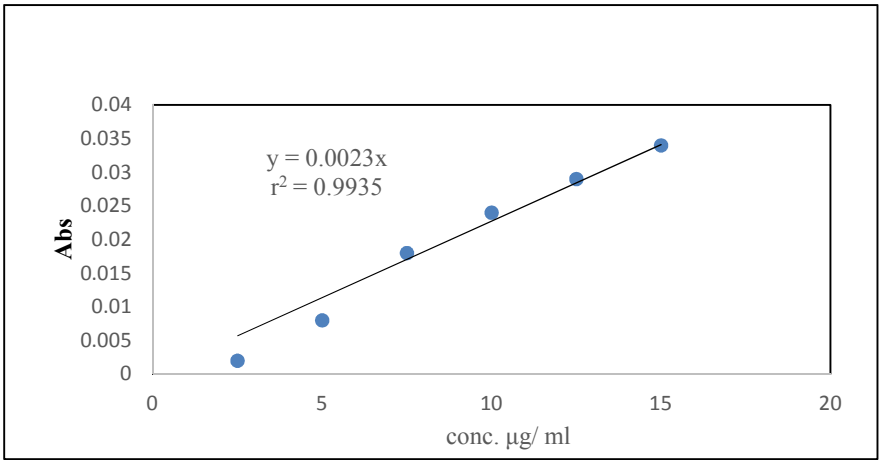

Fig. 13. Calibration curve of CAF at 272 nm

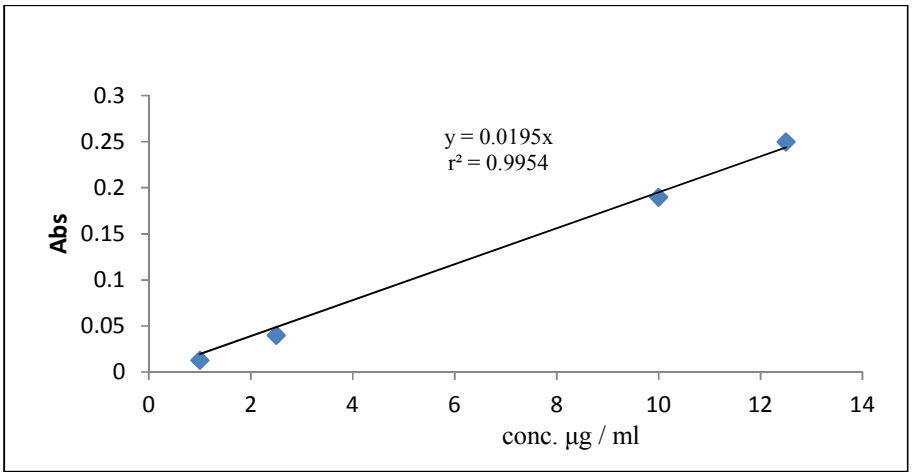

Fig. 14. First order derivative calibration curve of CAF at 213 nm

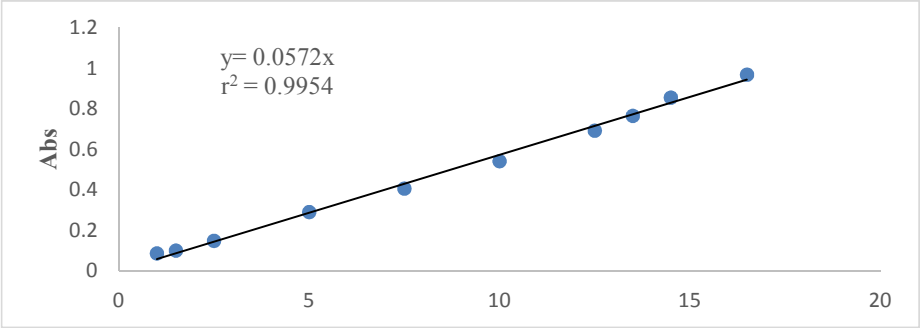

Fig. 15. Calibration curve of PAR at 257 nm

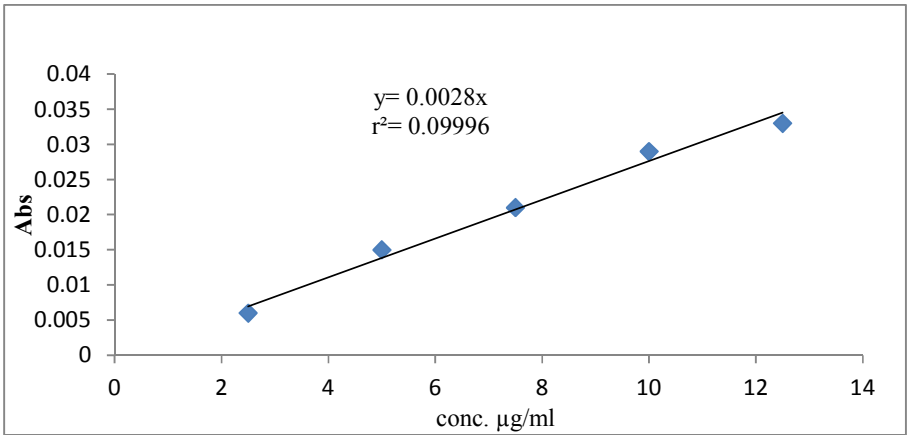

Fig. 16. First order derivative calibration curve of PAR at 230 nm

Table 1. Optical analytical parameters of proposed methods

Parameter	IBU	CAF	PAR
λ max.(nm)			
First method	220	272	257
First-order derivative	212	272	230
Linearity (μg/mL)			
First method	1-15	1-10	1-16.5
First-order derivative	1-15	1-13	2-13
Regression equation			
First method	Y=0.057x	Y=0.1215x-0.0022	Y=0.0572x
First-order derivative	Y=0.0023x	Y= 0.0195x	Y=0.0028x
Correlation coefficient (r^2)			
First method	0.9993	0.9920	0.9954
First-order derivative	0.9935	0.9954	0.9996
Slope			
First method	0.057	0.1215	0.0572
First-order derivative	0.0023	0.0195	0.0028
Intercept			
First method	000	-0.002	000
First-order derivative	000	000	000
LOQ (μg/mL)	2.105	0.987	2.097
LOD (μg/mL)	0.631	0.2962	0.629
Recovery %	99.13	100.18	99.7
RSD %	1.27	1.15	0.91

Table 2. Statistical validation for paracetamol at different levels of concentrations

Conc. Taken μg/mL	Conc. Found*μg/mL	Error%*	R.S.D%*	Recovery%*
2	1.98	1%	0.97	99%
6	5.95	0.83%	0.94	99.16%
10	10.1	1%	0.89	101%

**: mean of seven determinations, RSD: relative standard deviation*

Table 3. Statistical validation for Ibuprofen at different levels of concentrations

Conc. Takenμg/mL	Conc. Found*μg/mL	Error%*	R.S.D%*	Recovery%*
2.0	1.98	1%	1.21	99%
8.0	7.94	0.75%	1.31	99.25%
14.0	13.88	0.85%	1.29	99.14%

**: mean of seven determinations, RSD: relative standard deviation*

Table 4. Statistical validation for the caffeine at different levels of concentrations

Conc. Takenμg/mL	Conc. Found*μg/mL	Error%*	R.S.D%*	Recovery%*
2.0	2.01	0.5%	1.12	100.5
6.0	5.99	0.17%	1.13	99.83
9.0	9.02	0.22%	1.21	100.22

**: mean of seven determinations, RSD: relative standard deviation*

Table 5. Statistical validation for the standard mixture

Conc. Taken μg/mL	Conc. Found* μg/mL	Error%*	R.S.D%*	Recovery%*
Ibuprofen				
1.5	1.49	0.77	0.9	99.33
6.0	5.89	1.83	1.1	98.16
10.0	10.10	1.00	1.2	101.00
Caffine				
1.5	1.48	1.33	0.87	98.66
6.5	6.44	0.92	1.12	99.07
12.0	12.05	0.416	1.34	100.41
Paracetamol				
2.5	2.47	1.2	0.98	98.8
8.5	8.42	0.94	1.23	99.09
16.5	16.61	0.67	1.49	100.67

Table 6. Assay of No pain® capsules

Pharmaceutical preparation (No Pain)®	Proposed method	Standard method
	Mean Recovery %	Mean Recovery %
PAR 325 mg	98.58	97
IBU 200 mg	98.15	95
CAF 30 mg	98.66	98

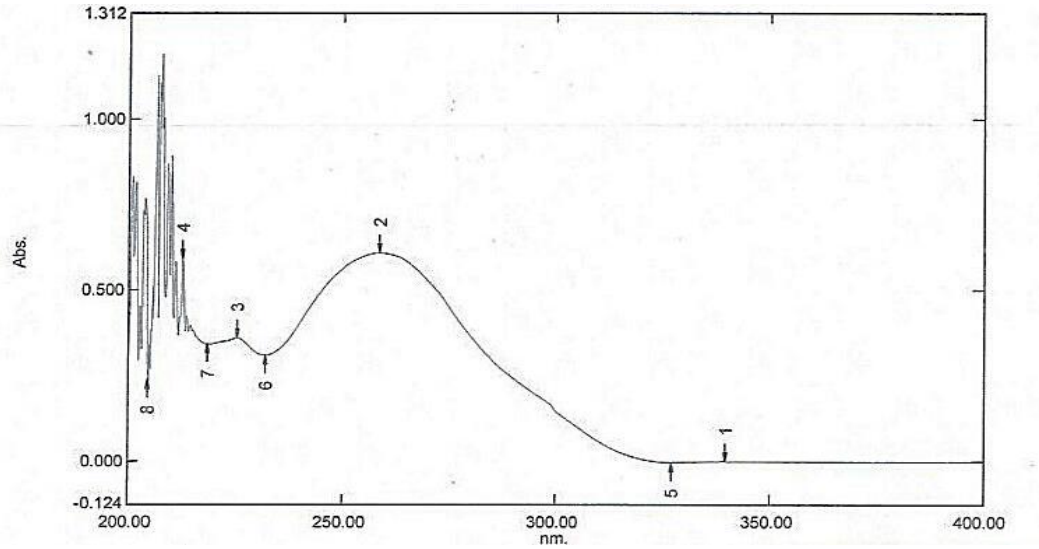

Fig. 17. Absorption UV spectra of sample (No Pain) ® the UV spectrum of (16.5 µg/ml, 10.0 µg/ml and 1.5 µg/ml) of PAR, IBU and CAF, respectively

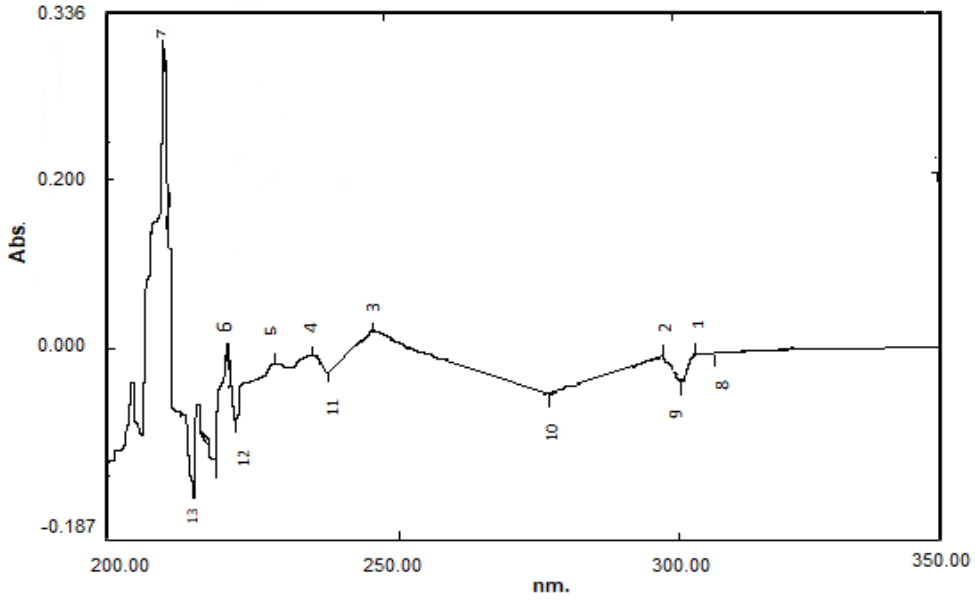

Fig. 18. First order derivative linearity spectra sample (No Pain) ® the UV spectrum of (16.5 µg/ml, 10.0 µg/ml and 1.5 µg/ml) of PAR, IBU and CAF, respectively

Table 7. Statistical validation for the commercial form (No Pain)® capsules

Conc. Taken µg/mL	Conc. Found*µg/mL	Error%*	R.S.D%*	Recovery%*
PAR 325 mg	320.4	1.41	0.87	97.75
IBU 200 mg	196.3	1.85	0.93	95.30
CAF 30 mg	29.6	1.33	0.97	96.66

**: mean of four determinations, RSD: relative standard deviation*

Table 8. Application of t and F –test for comparison between proposed and standard method

Pharmaceutical preparation	Proposed method		Standard method	
	Recovery %(Xi)1	$(Xi1-X1)^2$	Recovery % (Xi)2	$(Xi2-X2)^2$
PAR 325 mg	98.58	0.0144	97.75	1.3924
IBU 200 mg	98.15	0.0961	95.30	1.6129
CAF 30 mg	98.66	0.04	96.66	0.0081
	X1= 98.46	∑= 0.150	X2= 96.57	∑=3.0134

T value (exp.)= 2.607, Critical value=2.77
F value(exp.)= 0.049, Critical value=19.00

4. CONCLUSION

Simple, accurate and precise methods have been pronounced for simultaneous determination of Ibuprofen, Caffeine, and Paracetamol in pure and in the capsules dosage form. The methods were approved by examining the linearity, accuracy, precision, limit of detection and quantification. Further, according to statistical tests which are applied to evaluate the methods used, the results showed that the application of these methods is efficient for routine analysis, quality control of a mixture and marketing preparations comprising these three drugs.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENTS

The authors would like to thank Sammara laborateris for providing gift sample of Paracetmol, Ibuprofen and Caffaien. We are grateful the staff of pharmaceutical chemistry department, faculty of pharmacy for providing all neceasery facilites and support to carry out this work.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Adams SS. The propionic acids: A personal perspective. J Clin Pharmacol. 1992;32(4):317-323.
2. Grisales JO, Arancibia JA, Olivieri AC. Determination of enantiomeric composition of ibuprofen in pharmaceutical formulations by partial least-squares regression of strongly overlapped chromatographic profiles. J. Chromatogr. Biomed. Appl. 2012;910:78-83. DOI:10.1016/j.jchromb.
3. Mallet C, Eschalier A, Daulhac L. Paracetamol: Update on its Analgesic Mechanism of Action. In: Maldonado C.editor. Pain Relief-From Analgesics to Alternative Therapies..London: InTech; 2017.
4. Eccles R, Turner RB, Dicpinigaitis PVJL. Treatment of acute cough due to the common cold: Multi-component, multi-symptom therapy is preferable to single-component, single-symptom therapy—a pro/con debate. lung. 2015;194(1):15-20.
5. Atkinson HC, Currie J, Moodie J, Carson S, Evans S, Worthington JP, Steenberg LJ, Bisley E, Frampton CJ. Ejocp: Combination paracetamol and ibuprofen for pain relief after oral surgery: A dose ranging study. Eur. J. Clin. Pharmacol. 2015;71(5):579-587.
6. Dahl J, Nielsen R, Wetterslev J, Nikolajsen L, Hamunen K, Kontinen V, Hansen M, Kjer J, Mathiesen O, Scandinavica SPPAJAA. Post-operative analgesic effects of paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: A topical review. Acta Anaesthesiol Scand. 2014;58(10):1165-1181.
7. Sweetman SC. Martindale: The complete drug reference. 36th Editi. London: Pharmaceutical Press; 2009.
8. Burke A, Smyth E, Fitzgerald GA. Analgesic-antipyretic agents, pharmaco-therapy of gout. In: Brunton, L.L., Lazo, J.S. and Parker, K.L. editors. Goodman and Gilman. Pharmacological Bases of Therapeutics. 11th ed. New York: McGraw Hill Company Incorporation. 2006;671-715.
9. Kimiaei Asad H, Mohammad RJ, Arezoo S. Clinical trial of combination of

acetaminophen, ibuprofen and caffeine on pain relief and analgesic use after impacted lower third molar surgery. Shiraz E Med J. 2017;18(7):1-5.

10. Chandra R, Sharma KD. Quantitative determination of paracetamol and caffeine from formulated tablets by reversed phase-HPLC separation technique. Int J Chromatogr Sci. 2013;3(2):31-34.
11. Suryan AL, Bhusari VK, Rasal KS, Dhaneshwar SR. Simultaneous quantitation and validation of paracetamol, phenylpropanolamine hydrochloride and cetirizine hydrochloride by RP-HPLC in bulk drug and formulation. Int J Pharm Sci Drug Res. 2011;3(4):303-308.
12. Tsvetkova B, Pencheva I, Zlatkov A, Peikov P. Simultaneous high-performance liquid chromatography determination of paracetamol and ascorbic acid in tablet dosage forms. Afr J Pharm Pharmacol. 2012;6(17):1332-1336.
13. Viswanath RP, Useni RM, Varaprasad B, Somasekhar P. A novel RP-HPLC method for analysis of paracetamol, pseudoephedrine, caffeine and chlorpheniramine maleate in pharmaceutical dosage forms. Journal of Pharmacy Research. 2011;4(4):1225-27.
14. Tingting C,Qin Li, Jinmiao Lu, Chen Yu, Chao C, Zhiping Li, Determination of ibuprofen enantiomers in human plasma by HPLC–MS/MS: Validation and application in neonates. Bio-analysis. 2016;8(12):1237-1250.
15. Lou H-G, Yuan H, Ruan Z, Jiang B. Simultaneous determination of paracetamol, pseudoephedrine, dextrophan and chlorpheniramine in human plasma by liquid chromatography–tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2010;878(7-8):682–688.
16. Venkata R, Babu V, Pankaj KS. Gradient high performance liquid chromatography method development and validation for simultaneousdetermination of phenylephrine and ibuprofen in tablet dosage. Trop. J. Pharm. Res. 2014;13(6): 967-974.
17. Lakshmi NV, Anoop A. Determination of acetaminophen and caffeine using reverse phase liquid (rp-lc) chromatographic technique, J. Res. Pharm. Sci. 2016;3(4): 05-10.
18. Rajavel P. Development and validation for the simultaneous estimation of ibuprofen and codeine phosphate in tablet dosage forms by RP-HPLC. Asian J Pharm Anal Med Chem. 2013; 1(1):8- 17.
19. Maslarska V, Tencheva J. Simultaneous determination and validation of paracetamoland codeine phosphate in pharmaceutical preparation by RP-HPLC. Int. J Pharm Pharm Sci. 2013;5(2):417-419.
20. Sovan P, Sangeeta M, Gurudatta P, Jasmin P. Assay method development and validation of Ibuprofen in tablets by HPLC. Pharm. Sin. 2013;4(4):91-96.
21. Narendra N, Govinda SJ. Simultaneous estimation of Ibuprofen and famotidine in pure and combined dosage form by RP-HPLC. J. Appl Pharm Sci. 2012;2(5):79-83.
22. Wang HY, Kong AY, Yang B, Yan LP, Di X. Plasma ibuprofen enantiomers and their pharmacokinetics in Beagle dogs determined by HPLC. Acta Pharm. Sin. 2015;50(12):1607-1612.
23. Alothman ZA, Bukhari N, Wabaidur SM, Haider S. Simultaneous electrochemical determination of dopamine and acetaminophen using multiwall carbon nanotubes modified glassy carbon electrode. Sens Actuators B Chem. 2010; 146(1):314–320.
24. Akhgar MR, Beitollahi H, Salari M, Karimi-Maleh H, Zamani H. Fabrication of a sensor for simultaneous determination of norepinephrine, acetaminophen and tryptophan using a modified carbon nanotube paste electrode. Analytical Methods. 2012;4(1):259–264.
25. Alam AU, Qin Y, Howlader MMR, Hu NX, Deen MJ. Electrochemical sensing of acetaminophen using multi-walled carbon nanotube and β-cyclodextrin. Sens. Actuators, B Chem. 2018;254:896–909.
26. Sorina M, Florica M, Adriana L, Alberto MJ, Jorge G, Aniela P, et al. Electrochemical selective and simultaneous detection of diclofenac and ibuprofen in aqueous solution using hkust-1 metal organic framework-carbon nano fiber composite electrode, Sensors. 2016;16(10):1719.
27. Amin S, Soomro M, Tahir M, Najma S, Amber R, Sirajuddin Q. Disposable screen printed graphite electrode for the direct electrochemical determination of ibuprofen in surface water. Environmental Nanotechnology, Monitoring & Management. 2014;1-2:08-13.

28. Saeed S, Reyhaneh-Sadat S. voltammetric determination of acetaminophen in the presence of codeine and ascorbic acid at layer-by-layer MWCNT/hydroquinone sulfonic acid-over oxidized polypyrrolemodified glassy carbon electrode. Int. J. Electrochem. 2011;2011: 1-10.
29. Trettin AA, Zoerner, Böhmer A, Gutzki FM., Stichtenoth DO, Jordan J, Tsikas D. Quantification of acetaminophen (paracetamol) in human plasma and urine by stable isotope dilution GC–MS and GC–MS/MS as pentafluorobenzyl ether derivative. J Chromatogr B Analyt Technol Biomed Life Sci. 2011;879(23):2274-80.
30. Lou H-G, Yuan H, Ruan Z, Jiang B. Simultaneous determination of paracetamol, pseudoephedrine, dextrophan and chlorpheniraminein human plasma by liquid chromatography–tandem mass spectrometry. J. Chromatogr B. 2010;878:682-688.
31. Khorrami AR, Rashidpur A. Development of a fiber coating based on molecular sol–gel imprinting technology for selective solid-phase micro extraction of caffeine from human serum and determination by gas chromatography/mass spectrometry. Anal Chim Acta. 2012;727:20–25. DOI:10.1016/j.aca.2012.03.048.
32. Saeed AM. Spectrophotometric determination of paracetamol in some manufactured tablets in Iraqi markets. Int. J Pharm Sci Rev Res. 2017;42(2):53-57.
33. Ahmed M, Noor Q. Estimation of paracetamol, aspirin, ibuprofen, codeine and caffeine in some formulated commercial dosage using UV – spectroscopic method. Eur J Pharm Med Res. 2017;4(7):33-38.
34. Shahlaei M, Andisheh H, Derakhshandeh K, Havadi KS, Azami M. A novel method for simultaneous determination of codeine and acetaminophen in plasma by combination of UV-Vis spectroscopy and artificial neural network. J. Rep. Pharm. Sci. 2014;3(2):141-158.
35. Dobrinas S, Soceanu A, Popescu V, Stanciu G, Smalberger S. Optimization of a UV-vis spectrometric method for caffeine analysis in tea, coffee and other beverages. Sci. Study Res.: Chem. Chem. Eng. Biotechnol. Food Ind. 2013;14:071–078.
36. Navarra G, Moschetti M, Guarrasi V, Mangione MR, Militello V, Leone M. Simultaneous determination of caffeine and chlorogenic acids in green coffee by uv/vis spectroscopy. Journal of Chemistry. 2017;2017:1-8.
37. Glavanović S, Glavanović M, Tomišić V. Simultaneous quantitative determination of paracetamol and tramadol in tablet formulation using UV spectrophotometry and chemometric methods. Spectroscopy B. 2016;157:258-64.
38. Tehrani B Mirkamali, Souri E, Foroumadi A. Derivative spectrophotometric method for simultaneous determination of nickel(ii) and copper(ii) using 6-(anthracen-2-yl)-2,3-dihydro-1,2,4-triazine-3-thione. Asian J. Chem. 2012;24(10):4517-4521.
39. Souri E, Adel Mousavi S, Amanlou M, Tehrani B Maliheh. Development and validation of a rapid derivative spectrophotometric method for simultaneous determination of acetaminophen, ibuprofen and caffeine. Journal of Analytical Chemistry. 2015;70(3):333-338.
40. El-Zinati AM, Msjtoacj AL. Simultaneous determination of paracetamol and tramadol in pharmaceutical tablets by derivative UV-Vis absorption spectrophotometry. Analytical Chemistry Journal. 2015;8:1-6.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle3.com/review-history/46503