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Original Article

QUANTITATIVE ASSAY OF ASPIRIN AND (SALICYLIC ACID AND HEAVY METALS AS IMPURATIES) IN IRAQI'S MARKET ASPIRIN TABLETS USING DIFFERENT ANALYTICAL METHODS

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ABSTRACT

Objective: Easy and precise methods were developed for estimation of aspirin (ASP), impurities from such as salicylic acid (SAL) and heavy metal ions (HMI) in ASP tablets that available in the Iraqi's market using High-performance liquid chromatography (HPLC), UV–VIS spectrophotometry and atomic absorption spectrophotometric (AAS).

Methods: HPLC separation was carried out using C18 as stationary phase and acetonitrile (ACN): water in the ratio of (10: 90 v/v) as a mobile phase for HPLC method and as a solvent for UV-VIS spectrophotometric for quantitative ASP and SAL at 254 nm for HPLC, 226 and 296 nm for UV measurements. AAS was used for HMI determination.

Results: ASP and SAL gave absorbance maxima at 226 and 296 nm in ACN: H_2O solvent. The Beer's law was obeyed in the range of 0.05-20 for ASP and 0.02-8 µg/ml for SAL. Correlation coefficients (R^2) were 0.9996 and 0.9992 for ASP and SAL respectively, for HPLC and LOD value was 0.006 for ASP and 0.004 µg/ml for SAL. The % recovery for the developed method was found to be in the range of (98.80 to 101.26%) and (98.67 to 103.33%) for ASP and SAL respectively, within the acceptable range, that approved by world health organization (WHO).

Conclusion: The proposed method can help research studies, quality control and routine analysis with lesser resources available. The results of the assay of pharmaceutical formulation of the developed method are highly reliable and reproducible and is in good agreement with the label claim of the medicines.

Keywords: HPLC, Salicylic acid, Heavy metals, Aspirin tablets

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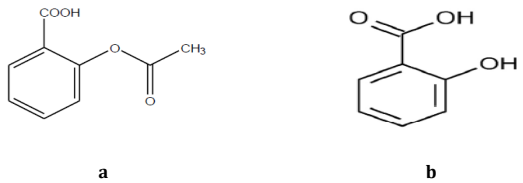
INTRODUCTION

In HPLC method there are several factors such as, the interaction between the solute components and the stationary phase that affected the chromatography resolution. HPLC is a good method for analysis of drugs because it has good selectivity and sensitivity values with small levels and in a complex matrix [1]. Therefore, the HPLC systems can be easily used to separate a wide range of chemical components. ASP is a nonsteroidal anti-inflammatory, antirheumatic, antithrombotic; chemically it is 2-acetoxy benzoic acid (fig. 1a) [2, 3]. In addition, aspirin is broadly used for the treatment of fever, inflammatory diseases, pain and blood thinner to prevent blood clots [4]. ASP is rapidly hydrolyzed in the body to produce salicylic acid (fig. 1b), which is the compound that is primarily responsible for the pharmacological activity of ASP. SAL is further metabolized to gentisic acid, salicyluric acid and other conjugates. It is not therapeutically active molecule as compare with ASP [5].



a b

Fig. 1: Chemical structure of aspirin and salicylic acid

An impurity in a drug substance as defined by the International Conference on Harmonisation (ICH) Guidelines, is any component of the drug substance that is not the chemical entity defined as the drug substance and affects the purity of active ingredient or drug substances [6]. The impurity profile of pharmaceuticals is of increasing importance as drug safety receiving more and more attention from the public and from the media. Therefore, identification, quantification, and control of impurities in the drug substance and drug product, are an important part of drug development and regulatory assessment [7]. Some evidences revealed that HPLC in particular mobile phase method was used to measure ASP and SAL in dosage forms or in biological materials [8-12]. The aim of this work is to develop a new analytical method, which consider to be an easy and applicable method to measure ASP and impurities in the aspirin tablets which are commercially available in Iraqi market pharmacy.

MATERIALS AND METHODS

Reagents and chemicals

ASP and SAL as pure standard powders were supplied by Sammara Drug Industries (SDI) Iraq. ASP tablets were obtained from local market. Acetonitrile (ACN), Methanol (HPLC-grade) and heavy metal ion solutions (AAS–grade) were from BDH. All chemicals and reagents were of analytical grade and double distilled water was used.

Instrumentation and analysis condition

Spectroscopic analysis was carried out using Jasco V-650 Japan double beam UV-Visible spectrophotometer with 10 mm path length quartz cells was used for the analytical purpose. The separation was achieved by using HPLC Shimadzu LC–20 A, Japan uses ACN: H_2O (10: 90) as mobile phase and Phenomenex C18 column (50 × 4.6 mm, 3µm). The separation was monitored for 5 min at 254 nm using a UV-visible detector and 1 ml/min flow rate. Atomic absorption AUORA Canadian model was used for HMI analysis.

Preparation of stock solutions of drugs (100 µg/ml)

Accurately weighed 0.01 g pure samples of ASP and SAL were transferred to 100 ml calibrated volumetric flask, dissolved and made

up to the mark with ACN: H_2O (10: 90 v/v). It was the stock solution of ASP and SAL (100 µg/ml) in ACN: H_2O. By using the stock solution of 100 µg/ml, subsequent dilution was carried out by withdrawing different aliquots (0.02-3.0 ml) from standard solution were transferred into a series of 10 ml calibrated volumetric flasks and all were made up to the mark with ACN: H_2O in order to prepare working standard solutions of different concentrations (0.02-30 µg/ml).

Procedure for drugs assay in pharmaceuticals tablets

Ten tablets of ASP drug's formula were weighed accurately and powdered finely. An accurately weighed quantity of tablets, powder equivalent to 100 mg of ASP was transferred to a 100 ml volumetric flask and diluted with (H_2O: ACN 90: 10 v/v), and the content was ultrasonicated for 20 min. The volume was made up to the mark with solvent and mixed well. The solutions were further filtered using whatman no. 1 filter paper to remove any unwanted particulate materials. The filtered solutions were further appropriately diluted with a respective solvent to finally produce a sample solution of concentration 10 µg/ml for analysis. The amount of ASP, SAL and heavy metal ions present in the sample solution was determined by using the calibration graphs of the standard.

RESULTS AND DISCUSSION

UV-VIS Spectrophotometry method

Estimation of detection wavelength

A solution of ASP and SAL mixture in the concentration of 10 µg/ml was scanned in the range of wavelength 200-400 nm [13]. It was observed that the ASP and SAL mixture showed considerable absorbance at a wavelength of 226 and 296 nm. The absorption spectrum was found sharp and maximum at a wavelength of 226 nm for ASP and at 296 nm for SAL. Therefore, it was selected as the wavelength for detection in (H_2O: ACN 90: 10 v/v). The study of spectrum revealed that ASP and SAL mixture shows a well-defined λ_{max} at 226 and 296 nm respectively as shown in (fig. 2).

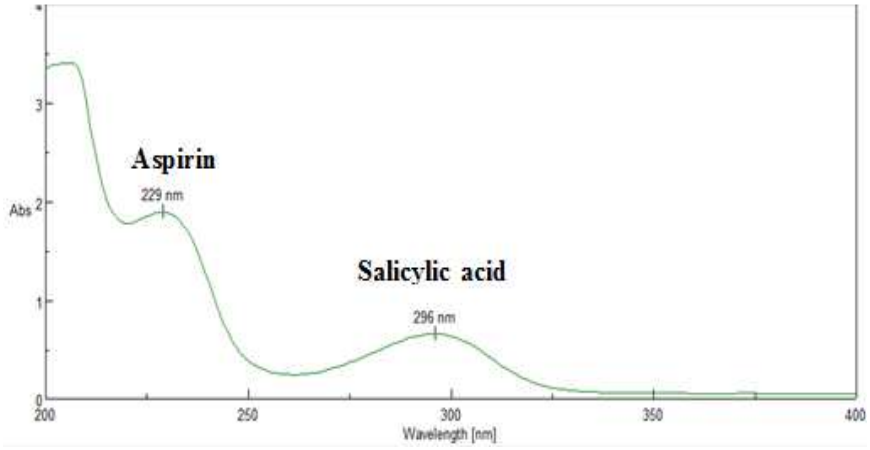


Fig. 2: UV–VIS spectrum of aspirin and salicylic acid mixture

Preparation of calibration graphs

The solutions of ASP and SAL standard mixture in different concentrations (0.05 to 30 and 0.02 to 8 µg/ml) for ASP and SAL respectively, were taken and the absorbance of these solutions were measured against solvent (H_2O: ACN 90: 10 v/v) as blank at a wavelength of 229 nm and 296 nm. A calibration graphs were constructed by plotting absorbance versus concentrations and a regression equations were calculated [14]. From the calibration graphs, it was found that ASP and SAL obeys Beer's law in concentrations of 0.3–30 and 0.1-10 µg/ml for ASP and SAL respectively, as shown in (fig. 3). Statistical parameters were calculated as shown in (table 1), revealed that the t_{cal} values were larger than the values of t_{tab}. Good linearity was observed with an R^2 of (0.9996 and 0.9992) for ASP and SAL respectively. The linear regression data for the calibration plot are indicative of a good linear relationship between concentration variation and response. Determined of linearity was done by regression analysis.

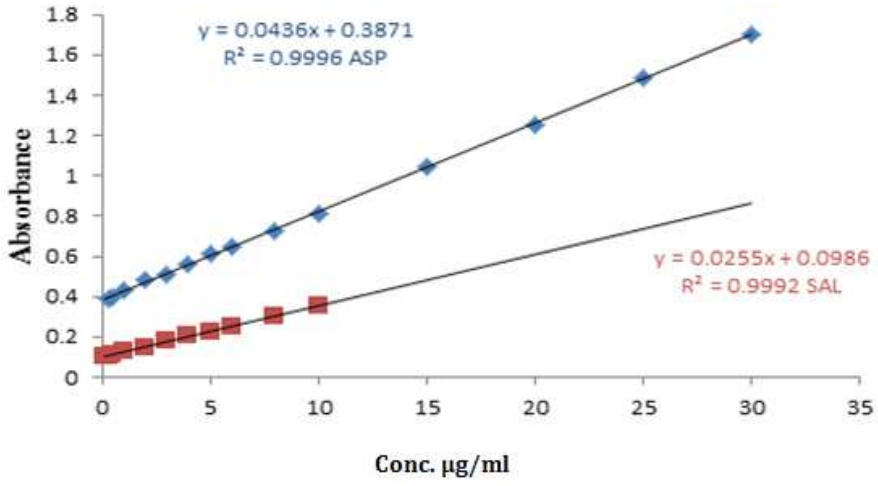


Fig. 3: UV–VIS calibration graphs of ASP and SAL mixture

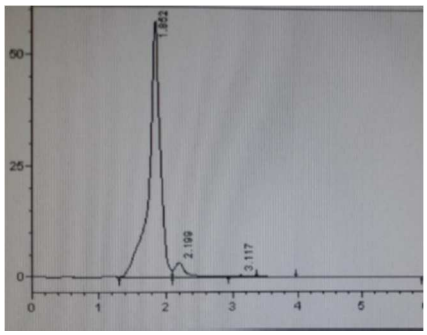
Table 1: Statistical parameters of UV-VIS determination of ASP and SAL

Statistical parameter	Value	
	Aspirin	**Salicylic acid**
Linear equation	y = 0.0436 [X]+0.3871	y = 0.0255 [X]+0.0986
Slope (m)	0.0436	0.0255
Intercept (b)	0.3871	0.0986
Correlation Coefficient (R^2)	0.9996	0.9992
Percentage Linearity (R^2%)	99.96	99.92
Intercept standard error	0.22	0.13
Intercept standard deviation	0.33	0.18
Relative standard deviation (RSD)	1.41	1.12
LOD (µg/ml)	0.09	0.03
Linearity range (µg/ml)	0.3-30	0.1-10
Calculated t-value	173.7>>2.14	106.04>>2.21

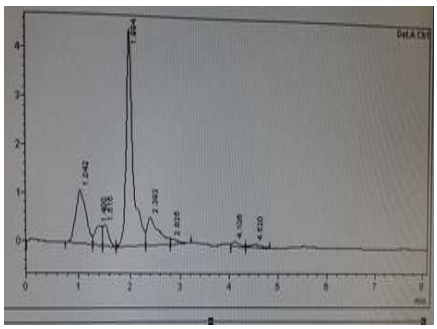
HPLC method

Chromatographic condition

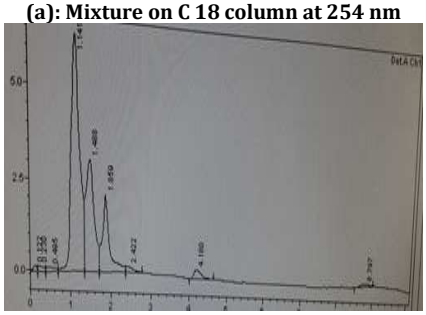
The RP-HPLC method was developed to provide specific procedure for the rapid quality control analysis of ASP and SAL. To find the appropriate HPLC condition for the separation of the examined drugs, various reversed-phase columns, isocratic mobile phase systems and different wavelength detection were tried and successfully attempts were performed using a Phenomenex C18 column (50 × 4.6 mm, 3µm) and a mobile phase composed of ACN: H_2O (10: 90) at a flow rate of 1 ml/min with λ_{max} at 254 nm. Injection volume was 20 µl and elution time was close to five min. various analytical columns were tested for obtaining good and reproducible response within the short run time. Under the described HPLC parameters, the respective compound was clearly separated and their typical chromatogram (fig. 4a), which shows a clear separation between the peaks at reasonable Rt 1.8 and 2.199 min using a C18 column in comparison with C8, which shows Rt higher than 2.199 and unclear chromatogram (fig. 4 b). Three selected detector wavelengths (254, 214 and 270 nm) were applied to estimate the separated compounds chromatograms as shown in (fig. 4 a, c and d). The results were indicated that the best chromatogram was obtained at 254 nm. HPLC separation of ASP and SAL had been carried out using various mobile phases consisting of water and (methanol or acetonitrile) as the organic phase. Fig. 4 (e, f and g) are shown the chromatograms of ASP and SAL standard analysis on C18 at 254 nm using different mobile phase ACN: H_2O and methanol: H_2O, which shown more Rt than1.8 and it means that developed method is more rapid.



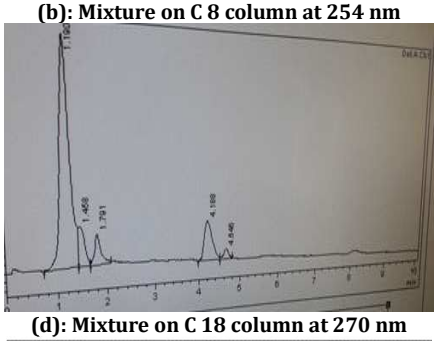
(a): Mixture on C 18 column at 254 nm



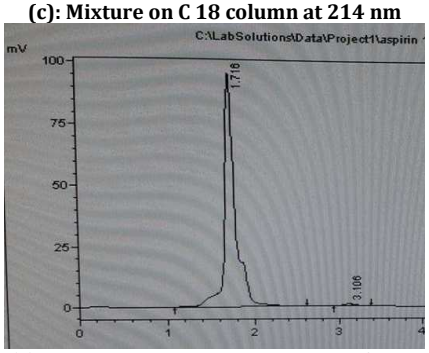
(b): Mixture on C 8 column at 254 nm



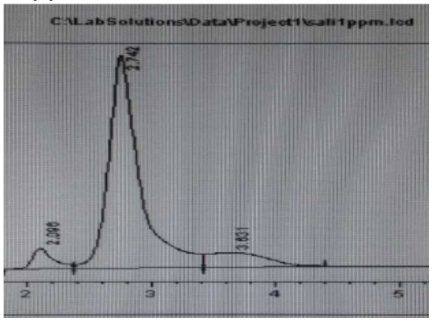
(c): Mixture on C 18 column at 214 nm



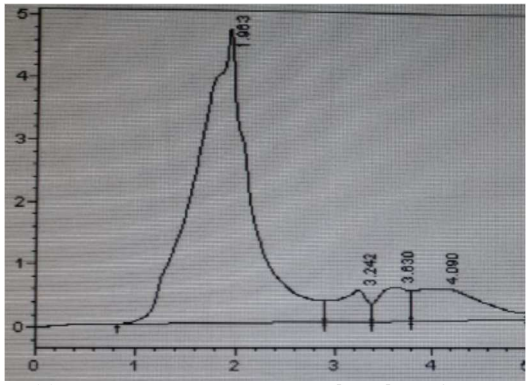
(d): Mixture on C 18 column at 270 nm



(e): ASP on C 18 using 10% ACN at 254 nm



(f): SAL on C 18 using 10% ACN at 254 nm



(g): ASP on C 18 using 10% methanol at 254 nm

Fig. 4 (a–g): Chromatograms of ASP, SAL and mixture using different condition

HPLC calibration graphs

Calibration graph representing the relation between the concentrations of drugs versus the peak area was constructed. A 20 µl of the standard solutions contain ASP or SAL were injected in triplicate run from which the linear regression equation was calculated. A calibration graphs were constructed by plotting area under peak versus concentrations and a regression equations were calculated. The results of chromatographic determination are presented in table 2, which shown that the linear dynamic range for aspirin was in the range 0.05-20 µg/ml, while for salicylic acid was 0.02-8 µg/ml as shown in (fig. 5). The statistical analytical values such as correlation coefficient (R^2), limit of detection (LOD) and other parameters for HPLC methods were tabulated in table 2. Good linearity was observed with an R^2 of (0.9993 and 0.9992) for ASP and SAL respectively. The linear regression data for the calibration plot are indicative of a good linear relationship between concentration variation and area.

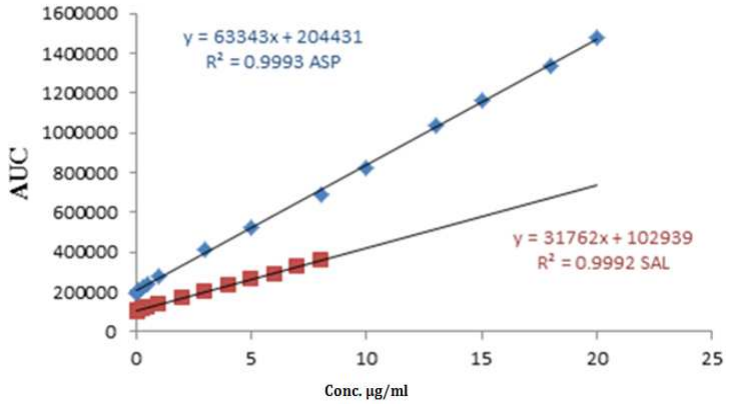


Fig. 5: Calibration graphs of ASP and SAL using HPLC

Table 2: Statistical parameters of HPLC determination of ASP and SAL

Statistical parameter	Value	
	Aspirin	Salicylic acid
Linear equation	y = 63343 [X]+204431	y = 31762 [X]+10293
Slope (m)	63343	31762
Intercept (b)	204431	10293
Correlation Coefficient (R^2)	0.9993	0.9992
Percentage Linearity (R^2%)	99.93	99.92
Intercept standard error	8957	4953
Intercept standard deviation	23794	14251
Relative standard deviation (RSD)	2.36	2.21
LOD (µg/ml)	0.006	0.004
Linearity range (µg/ml)	0.05-20	0.02-8
Calculated t-value	130.87>>2.14	111.78>>2.18

Accuracy, precision and recovery of proposed methods

This study was carried out to assure the closeness of the test results obtained by the analytical method to the true value [15]. For study methods ASP and SAL were determined at three different selected concentrations within the Beer's law limits 10, 15, 20 and 0.3, 1.0, 1.5 µg/ml for ASP and SAL respectively, using UV-VIS spectrophotometry, while 5, 10, 15 and 0.08, 0.5, 1.0 µg/ml for ASP and SAL respectively by HPLC method. The results were reported as % Recovery, % Error and % RSD, as in table 3, which revealed that the suggested method for detection of aspirin and salicylic acid were interesting and quite convenient with respect to the methods and parameters calculated.

Table 3: Accuracy and precision of proposed methods

UV-VIS				
ASP (µg/ml) % recovery			**%Error**	**%RSD (n = 3)**
Taken	**Mean found±SD (n=3)**			
10	10.06±0.014	100.06	0.06	0.14
15	15.13±0.016	100.87	0.13	0.11
20	19.96±0.029	99.80	0.20	0.15
SAL (µg/ml)				
Taken	**Mean found±SD (n=3)**			
0.3	0.31±0.0003	103.33	3.33	0.10
1.0	1.01±0.0017	101.00	1.00	0.17
1.5	1.48±0.0024	98.67	0.33	0.16
HPLC				
ASP (µg/ml)				
Taken	**Mean found±SD (n=3)**			
5	4.99±0.0085	99.80	0.20	0.17
10	10.02±0.008	100.20	0.20	0.08
15	15.19±0.018	101.26	1.26	0.12
SAL (µg/ml)				
Taken	**Mean found±SD (n=3)**			
0.1	0.099±0.0001	99.66	0.34	0.10
0.5	0.499±0.005	99.80	0.20	0.01
1.0	1.004±0.0009	100.40	0.40	0.09

Values represent mean±SD, n=3.

Table 4: The obtained results of ASP and SAL in pharmaceutical tablets

Company	**Aspirin weight (mg)**	**Mean found of ASP (mg)±SD (n = 3)**		**% recovery**		**% salicylic acid ±SD (n = 3)**	
		UV-VIS	**HPLC**	**UV-VIS**	**HPLC**	**UV-VIS**	**HPLC**
Cox-pharmaceutical Ltd.	75	74.25±0.53	74.36±0.61	99.00	99.15	0.111±0.002	0.108±0.001
Dijla-IRAQ	100	100.90±1.78	99.94±1.45	100.90	99.94	0.101±0.001	0.102±0.001
Adiphram	100	100.05±1.04	100.00±0.99	100.05	100.00	0.102±0.001	0.100±0.002
SDI-IRAQ	100	99.85±1.22	100.03±1.11	99.85	100.03	0.113±0.003	0.103±0.002
Bristol laboratories Ltd	75	74.5±0.66	75.01±0.44	99.33	100.01	0.101±0.001	0.102±0.001
Wockhardt UK	300	299.4±1,98	300.04±1.88	99.80	100.01	0.123±0.011	0.121±0.003
Aswar alkhaleje–IRAQ	100	101.30±1.34	99.91±1.14	101.30	99.91	0.109±0.001	0.103±0.002
BAYAR	81	80.60±0.88	81.02±0.77	99.50	100.02	0.099±0.001	0.107±0.001
MOH-IRAQ	100	99.80±0.98	100.21±0.88	99.80	100.21	0.099±0.001	0.095±0.001
ATABAY-Turkey	80	82.08±0.87	80.06±0.67	102.60	100.07	0.103±0.001	0.111±0.003
ASIA-Syria	81	81.25±0.77	81.00±0.55	100.31	100.00	0.112±0.002	0.102±0.001
Medcellpharma–Nether.	100	99.05±1.01	100.15±0.99	99.05	100.15	0.109±0.002	0.108±0.001
Pharmaline-Lebanon	100	102.03±1.35	101.27±1.21	102.03	101.27	0.099±0.001	0.098±0.001
Actavis	300	301.80±1.89	304.54±1.11	100.60	101.51	0.120±0.003	0.119±0.002
Antibiotic SA-Romania	100	98.98±1.02	99.76±1.03	98.98	99.76	0.105±0.001	0.109±0.002
Rameda–Egypt	75	74.60±0.76	74.78±0.71	99.46	99.71	0.115±0.002	0.116±0.002
BAYAR	100	100.01±1.12	100.65±1.01	100.01	100.65	0.100±0.001	0.099±0.001
Sunlond-Atlanta	81	81.09±0.81	80.91±0.76	100.11	99.89	0.112±0.002	0.101±0.001
Cisphrama-USA	81	80.95±0.75	80.25±0.66	99.93	99.07	0.099±0.001	0.101±0.002
Allegiant Health	81	80.64±0.73	81.23±0.72	99.55	100.28	0.113±0.002	0.111±0.003

Values represent mean±SD, n=3.

Table 5: The amount of heavy metals measured by AAS

Company	**Pb found at 283 nm (µg/kg) n =3**	**Co found at 210 nm (µg/kg) n=3**	**Fe found at 248 nm (µg/kg) n=3**	**Ni found at 232 nm (µg/kg) n=3**	**Cd found at 228.8 nm (µg/kg) n=3**	**Cr found at 357.9 nm (µg/kg) n=3**
Cox–pharmaceutical Ltd.	12.1	1.2	12.1	6.2	8.9	6.2
Dijla-IRAQ	7.2	1.4	12.2	6.5	7.2	6.5
Adiphram	10.4	1.2	10.4	7.2	8.3	7.2
SDI-IRAQ	10.5	1.3	10.5	5.4	7.8	5.4
Bristol laboratories Ltd.	10.6	1.1	10.6	3.8	8.8	3.8
Wockhardt UK	7.5	1.3	9.5	5.5	7.5	5.5
Aswar alkhaleje–IRAQ	7.8	1.4	9.8	4.6	7.8	4.6
BAYAR (81)	10.0	0.9	10.0	3.2	3.5	3.2
MOH-IRAQ	10.2	1.1	10.2	5.1	8.4	5.1
ATABAY-Turkey	10.8	1.5	10.8	5.6	5.6	7.6
ASIA-Syria	10.9	1.4	10.9	6.6	7.7	6.6
Medcellpharma–Nether.	6.9	1.2	9.9	4.6	6.9	4.6
Pharmaline-Lebanon	11.3	1.3	11.3	3.6	5.3	3.4
Actavis	8.6	1.0	8.6	6.3	8.6	6.3
Antibiotic SA-Romania	12.0	1.4	12.0	6.7	8.8	7.6
Rameda–Egypt	6.7	1.2	9.7	5.8	2.6	5.8
BAYAR (100)	10.3	1.3	10.3	2.3	4.4	2.3
Sunlond-Atlanta	8.4	1.0	8.4	2.1	8.4	2.4
Cisphrama-USA	8.1	1.0	8.1	2.3	8.1	2.2
Allegiant Health	10.7	1.1	10.7	3.4	6.7	2.3

Values represent mean only n =3.

Quantitative assessment of ASP and SAL in tablets

Twenty pharmaceutical drugs that contain aspirin were commercially available in Iraqi markets. In table 3, we mentioned the names of the companies that we used their products to detect aspirin and salicylic acid. Table 4, represents the data we was obtained from our recommended and suggested method. Interestingly the results were suggested the precision and the appropriateness of the suggested method to determine of ASP and SAL in pharmaceutical tablets. Furthermore, the data were revealed that the recovery percentages for applying methods are with an acceptable range of the medication samples and the amount of the salicylic acid was within the standard and accepted percentage as compared to official analytical method [16, 17]. Therefore, we used recovery percentage in formulating tablets as indicating the validity of the method for analysis the aspirin and the impurities of salicylic acid in pharmaceutical formulation. RSD for all results is less than 2%.

Atomic absorption spectrophotometry

The heavy metals contain in aspirin tablets, such as Nickel, Cobalt, Iron, Lead, Cadmium and Chromium ions were determined by atomic absorption spectrophotometry. We summarized the results in table 5. Interestingly the data reveal that the amount of these metals within the normal ranges adopted by WHO [18].

CONCLUSION

The developed analytical methods were found to be simple, sensitive, rapid, economical, linear, reproducible and applicable over a wide concentration range with high precision and accuracy. The method was found suitable to determine the concentration of ASP as well as in the dosage form analysis precisely and accurately. The sample recovery from the formulation by using this method was very applicable in respect to its label claim. The results of the validated parameters were found to be satisfactory and can also be applied for the quality control tool in the estimation of aspirin, salicylic acid and heavy metal ions in pharmaceutical dosage forms.

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AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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