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Development and Validation of a Simple and Sensitive Reverse-Phase High Performance Liquid Chromatographic Method for the Determination of Ibuprofen in Pharmaceutical Suspensions

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Abstract:

The aim of this work was to develop and validate a rapid and low cost method for estimation of ibuprofen in pharmaceutical suspensions using Reverse-Phase High Performance Liquid Chromatography. The proposed method was conducted and validated according to International Conference on Harmonization (ICH) requirements. The chromatographic parameters were as follows: column of octyldecylsilyl C18 with dimensions (150 × 4.6) mm, mobile phase composed of acetonitrile with phosphoric acid with a ratio of 50 to 50 each using isocratic mode, flow rate of 1.5 mL/min and injection volume of 5 µL. The detection was carried out using UV detector at 220 nm. The method was validated and showed short retention time for ibuprofen peak at 7.651 min, with linearity in the studied range of 0.4 - 1.6 mg/mL (R^2 = 0.9999) and with great accuracy [percent recovery was (100.48%), percent relative error(-1.511-1.465)%] and repeatability (RSD% = 0.112 for Retention time). The detection and quantitation limits were determined to be 0.036 and 0.110 mg/mL, respectively. This method was applied successfully to determine the content of ibuprofen in three commercial pharmaceutical products. Looking at the short time of analysis and the low limit detection, we recommend this method for routine assays in the quality control laboratories and as a good method for stability studies of ibuprofen.

Keywords: Developed, Ibuprofen, Method validation, RP-HPLC, Suspension.

Introduction:

Ibuprofen (IBP); (±)-2-(p-isobutylphenyl) propionic acid was the first propionic acid derivative during the late 1960s [1]. Fig.1 illustrates the chemical structure of ibuprofen [2]. Because of its analgesic, antipyretic, and anti-inflammatory characteristics, IBP is one of the most commonly prescribed Non-Steroidal Anti-Inflammatory Drugs (NSAID) as Over-The-Counter (OTC) [3,4]. It is used to treat a variety of conditions, including pain and inflammation such as headaches, muscle discomfort, toothaches, fever, backaches, and dysmenorrhea [5,6].

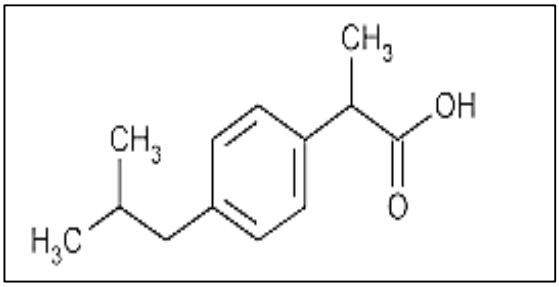

Figure 1. The chemical structure of Ibuprofen [2]

In comparison to aspirin, it is rather safe, and it has a higher efficacy than acetaminophen, so it is widely used to treat fever and pain in pediatric patients (5–10 mg/kg every 6–8 h) [3,7]. IBP has pharmacological effects by inhibiting cyclooxygenase-1 and 2 (COX-1 and COX-2) in a

reversible manner, so the synthesis of prostaglandin precursors is reduced as a result of this [8].

IBP can cause stomach irritation as a side effect due to its carboxylic moiety, so the ibuprofen ester can sometimes be prepared, which is considered prodrug that can prevent the side effect of ibuprofen which causes peptic ulcer. [9]

There are a lot of pharmaceutical forms of IBP including: Ibuprofen Gel, Oral Suspension Ibuprofen, Tablets Ibuprofen, Tablets Ibuprofen Prolonged-release, Capsules Ibuprofen Prolonged-release [10].

Literature survey showed different methods for analyzing and determining of IBP in oral suspension as volumetric assay [11], UV spectrophotometry [12], and HPLC methods [13]. There are some challenges when analyzing:

- Long retention time and high cost methods is not suitable for routine quality control (QC) analysis.
- The need to diminish the use of organic solvents. [14]
- The necessity to develop stability-indicating analytical method (SIAM) with low limit of quantification (LOQ).
- Large quantity of the studied samples need to be analyze daily.

According to IBP suspension monograph in British Pharmacopeia (BP) 2019, the assay method needs to column of C18(300 mm × 4 mm), so the analysis will be long and take more solvents. Therefore, to overcome these difficulties and to save time and solvents, the current study focused on the development of a simple, precise, sensitive, quick, economical, and accurate Reverse-Phase High Performance Liquid Chromatographic (RP-HPLC) method for analyze IBP easily in suspension dosage form.

According to International Conference on Harmonization (ICH), it recommends that ICH Q1(R2) guidelines be used to validate an analytical method when making changes in analytical procedure in order to confirm the method applied and to demonstrate that it is appropriate for its intended purpose [15]. The validation of method requires testing of parameters such as linearity, specificity, accuracy, precision.

The aim of this work was to develop and validate a rapid and low cost method for estimation of ibuprofen in pharmaceutical suspensions using Reverse-Phase High Performance Liquid Chromatography.

Materials and Methods:

Materials

Ibuprofen Chemical Reference Substance with impurity of 99.7%, (India). Acetonitrile gradient grade for liquid chromatography, Merck KGaA, (Germany). Phosphoric acid for liquid chromatography, Merck KGaA, (Germany). Commercial oral suspensions of ibuprofen 100 mg/5mL (each 5mL of suspension contains 100mg of ibuprofen) from three Syrian pharmaceutical companies (Unipharma, Avenzor, Bahri) named (A, B, C), respectively.

Instruments

Analyses carried out using a HPLC device (type: SHIMADZU LC-20ATprominence, Japan) with a column of octadecylsilica (ODS) C18 (150 mm length × 4 mm width) equipped with an isocratic pump and the tests were conducted at ambient temperature. Detection was carried out with a UV-detector with a wavelength 220 (nm). Homogenization process was done using ultrasonic bath (JEKEN modelPS-80A), USA and magnetic stirrer (VELP scientifica), USA. Weighing materials were done by Sensitive analytical balance (Sartorius model ED224-S), Germany.

Chromatographic Conditions

After a number of optimization trials had been carried out, in which various mobile phase ratios, columns with different dimensions several flow rates were tested, the proper conditions for the study were chosen, with the following details: HPLC device with auto sampler was the instrument used in this study with a UV-detector. The analysis was carried out at room temperature. ODS C18 (150 × 4.6) mm as a column. Acetonitrile: phosphoric acid with ratio of (50:50 v/v) as a mobile phase. 1.5 mL/min as a flow rate. The wavelength used was 220 nm. Retention time: 7.651 min.

Solvent preparation (mobile phase preparation)

0.3 mL of concentrated phosphoric acid with a concentration of 85% was taken in a glass beaker and the volume was supplemented to 500 mL with distilled water, and homogenization process was conducted using the magnetic stirrer for a 15 min, this gives a solution of phosphoric acid (0.06%v/v). Then, 500 mL of acetonitrile was added and well homogenized. As a result, the solvent is a 50:50 mixture of acetonitrile and prepared solution of phosphoric acid (0.01 M) respectively. Finally, the solution was filtration.

Stock standard solution preparation

A volumetric flask of 100 mL capacity was taken, carefully weighed 1000 mg of standard ibuprofen was dissolved in an amount of prepared solvent (acetonitrile: phosphoric acid), following the processes of stirring and homogenization by

ultrasound and magnetic stirrer, then adding solvent to the volume until it reaches the ultimate volume line. The resulting concentration was 10 mg\mL, which was 1000% of the target concentration (the target concentration of standard ibuprofen solution = 1 mg/mL).

Method validation

The developed analytical method has undergone method validation to ensure that it meets the intended requirements as described in the guidelines. The findings of the method validation can be used to determine the reliability, dependability and consistency of the developed method. The proposed method has been verified using the Q2 (R1) recommendations from the International Harmonization Conference (ICH) and the USP validation guidelines [15,16]. (Q2: Quality guidelines for Validation of Analytical Procedures: Text and Methodology).

Test for system suitability

Using standard solution (1 mg/mL) of IBP which was prepared from stock solution, the suggested method was tested for system suitability. This solution was injected six times. Parameters of the resolution, theoretical plates, tailing factor were assessed as results of system suitability with calculating percent relative standard deviation (RSD%) of six replicate injections. RSD% of no more than 2% was recommended. Retention time was also observed [17].

Linearity

Seven concentrations were prepared within the range of (0.4-1.6) mg/mL and the ratio range 40,60,80,100,120,140,160% of the target concentration (1 mg/mL). These solutions were injected under the improved method conditions, and the peak area response was shown against concentrations of the prepared standard series. By computing the slope, correlation coefficient, and intercept, the linear relationship between the area under the curve (AUC) and concentration was examined. For the calibration curve, a correlation of above 0.9999 was sought [18,19].

Precision

Precision was determined on the foundation of closeness between the observed results. Six 100% solutions were prepared at a concentration of 1 mg/mL of the stock solution by taking 5 mL of the stock solution into a 50 volumetric titration balloon and then completing the volume up to the titer line used the same solvent. These solutions were injected into HPLC device, as the result; AUC was noted. The mean, Standard deviation and the percent relative standard deviation (RSD%) were calculated [20]. The test was carried out intra-day and inter-day with the same way.

Accuracy

Three different concentration levels of standard stock solution were chosen to evaluate the accuracy of the method: 80 %, 100 %, and 120 %. Thus, we get the concentrations (0.8, 1, 1.2) mg/mL, respectively, then the prepared solutions were injected with three replicates for each concentration, i.e. 9 injections were injected. The results were represented as a percentage of recoveries, and the percent recovery mean was determined, where the ICH Q1(R2) recommendations outlined that the accuracy percent results be equal the value %100±2 in order for the test to be considered acceptable [21]. The accuracy was also estimated by calculating percent relative error which should be not more 5% [22].

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

The sensitivity of the method is determined by the LOD and LOQ values.

(LOD)

It's the tiniest amount of an analytic that can be identified, yet it's not always quantifiable. It was computed by the equation (1) [15] ;

$$LOD = \frac{3.3\,\sigma}{S} \qquad 1$$

Where; σ= the standard deviation of the response.
S = the slope of the calibration curve

LOQ

It's the smallest amount of analytic in a sample that can be measured with sufficient accuracy and precision. It was computed by the equation (2) [15] ;

$$LOQ = \frac{10\,\sigma}{S} \qquad 2$$

Where; σ = the standard deviation of the response.
S = the slope of the calibration curve.

Specificity

The specificity of the analytical method is evaluated by the analytical method which is unaffected by the presence of impurities or excipients and ensures that the peaks are free of interference by demonstrating the lack of interference with the analyte elution. In the same way as before, a 100% standard solution of reference IBP was made. A sample from suspension that containing the same concentration of IBP with excipients (Glycerine, Methyl praben sodium, propyl paraben sodium, sorbitol, Avicel, kaoline) was prepared by taken 5 mL of this suspension into a volumetric flask and then the volume was completed to the mark with the prepared solvent with the homogenization process, this solution was filtered through a 0.45µ syringe filter and was injected into the HPLC device. All measurements were repeated three times. Then the retention times and RSD% were observed. Method specificity was

assessed by comparing the resulting chromatograms as the excipient substances must not interfere with the analysis of the intended analytic [16,18].

Quantitative analysis of IBP in pharmaceutical suspension using the developed method

After shaking the suspension, a sample of 5 mL (equivalent to 100 mg IBP) from suspension (A) was moved to a volumetric flask with a capacity of 100 mL, then the volume was completed to the mark with the prepared solvent (acetonitrile: phosphoric acid) with sonication for 15 minutes to get homogeneous solution (which gives 1 mg/mL solution). Finally, this solution was filtered through a 0.45µ syringe filter and was injected into the HPLC device. A sample of suspension (B) and (C) was also prepared in the same way. The amount contained in the pharmaceutical product was calculated as a percentage and compared with the labeled quantity on the container. Each sample was analyzed in triplicate.

Statistical analysis:

The outcomes were analyzed using Microsoft Excel software 2010, where mean, standard deviation (SD), and the relative standard deviation (RSD) were computed for system suitability test, precision, and accuracy. Correlation coefficient was also computed for the parameter of linearity.

Results and Discussion:

In this study, a simple and appropriate RP-HPLC method was developed for estimating IBP, which allows analysis of more samples of ibuprofen suspension at short time during production. This improved method (column C18; 150 mm×4.6 mm, mobile phase: 50:50; acetonitrile: phosphoric acid 0.06%, retention time 7-8 min) is based on a British pharmacopeia RP-HPLC method (column C18; 300mm×3.9 mm, mobile phase: 40:60; acetonitrile: phosphoric acid, retention time 7-8 min), so it saves solvents and time, and could be employed in pharmaceutical QC facilities for routine analysis.

At first, the ratio of the mobile phase of the BP assay method (60:40; acetonitrile: phosphoric acid 0.01 M) was modified because this ratio given retention time of IBP between 15-19 min (Fig. 2). Several polarity ratios of phosphoric acid and acetonitrile (60:40, 55:45, 50:50, 45:55) were investigated by assessing IBP peaks, sharpness, peak symmetry and retention time to determine the best mobile phase ratio. The best results were obtained using a 50:50 mixture of acetonitrile and prepared phosphoric acid solution. This ratio ensured a faster elution of ibuprofen and led to appearing the retention time of the peak in less time. This result is due to the properties of ibuprofen which is characterized as relatively weak acid (pka 4.4), very low solubility in water or acid, and better soluble in organic solvents that lead to weak retention in column [23].

Various flow rates were examined. The flow rate of 1.5mL /min was chosen as the best for the research, knowing that the symmetry of the IBP peak was maintained.

Several C18 columns with different geometrics parameters were evaluated for their efficiency in the suggested method. The peak shape of the IBP that appeared at a lower time using the C18 column (150 mm× 4.6 mm) was acceptable and satisfactory. Therefore, this C18 column was chosen for the presented method of IBP estimation.

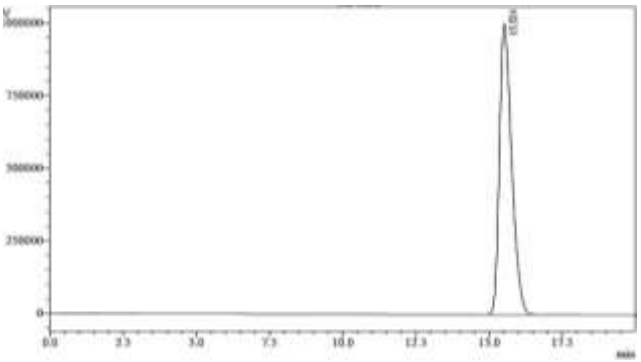

Figure 2. Chromatogram of the standard Ibuprofen resulting from the ratio (40:60) of acetonitrile and phosphoric acid according to the British Pharmacopoeia.

Method validation

System suitability

The test of system suitability is frequently employed as a control strategy, and it is an important part of the HPLC method. For the proposed method, the retention time and AUC for each injection were determined and RSD% was calculated. System suitability results: the retention time of IBP standard was 7.651 min (RSD% value of 0.022%), the RSD% of AUC was 0.036% and both are less than 2% which are totally acceptable, theoretical plate (5907.5±0.025), and tailing factor (1.331±0.02), so the outcomes were deemed acceptable. The results of the system suitability for the standard injections are summarized in Table 1, and the chromatogram of the standard ibuprofen solution is shown in Fig. 3.

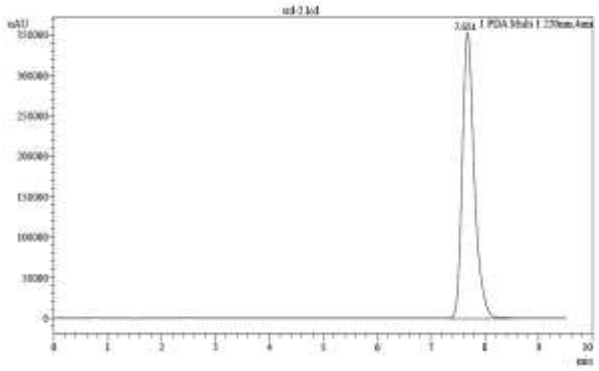

Figure 3. The chromatogram of the standard Ibuprofen solution with concentration of 1 mg/mL, using the ratio of acetonitrile and phosphoric acid (50:50)

Table 1. The results of System suitability.

System suitability		
Sample no	**peak area (mV/cm^2)**	**Retention time(min)**
1	5409308	7.651
2	5409730	7.65
3	5405271	7.649
4	5405509	7.653
5	5409308	7.654
6	5407947	7.651
Mean	5407845.5	7.651
SD	1996.3335	0.0017
RSD%	0.0369	0.022
Theoretical plates	0.025 ± 5907.5	
Tailing factor	1.331 ± 0.02	

Linearity

Over the studied range (0.4-1.6) mg/mL, a linear relationship was observed between peak area and IBP concentration. The mean linear regression equation was y= 5304751.3513x + 120795.3214. A study of the calibration curve revealed a high linearity coefficient R^2: 0.9999 (closer to 1) and is considered constitutionally acceptable value, which indicates the linearity of the method on the studied range. Table 2 summarizes the results, and Fig. 4 shows the graph produced by the standard ibuprofen series (linearity of Ibuprofen).

Table 2. Results of Ibuprofen standard series injections (Linearity) .

Sample no	Theoretical Concentration%	Concentration (mg/mL)	eak area (mV/cm^2
1	40%	0.403	2265620
2	60%	0.605	3336564
3	80%	0.807	4407352
4	100%	1.009	5441529
5	120%	1.211	6579784
6	140%	1.413	7624024
7	160%	1.615	8680433
linear regression equation			**y = 5304751.3513x + 120795.3214**
Linearity coefficient (R^2)			**R^2 = 0.9999**

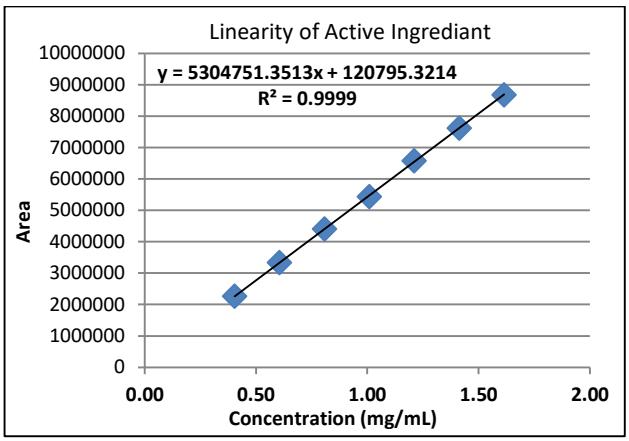

Figure 4. The calibration curve of Ibuprofen (linearity of Ibuprofen).

Precision

To assess the precision of the method, the six prepared solutions of ibuprofen were injected and the resulting response was recorded intra-day (repeatability) and inter-day (reproducibility). RSD% of retention time and area under the curve were calculated, as the results 0.112%, 0.0939% respectively as for repeatability. For reproducibility; RSD% were 0.284%, 0.890 % for area peaks and retention times respectively and both are less than 2%. Therefore, the % RSD obtained in relation to method precision results met the admission criteria (no more than 2%) and give the analytical method an excellent precision. Table 3 and Table 4 show the results of the repeatability and intermediate precision of the analytical method for ibuprofen, respectively.

Table 3. Results of a Repeatability of the analytical method for Ibuprofen.

Repeatability		
Sample no	**peak area (mV/cm^2)**	**Retention time(min)**
1	5437872	7.678
2	5436336	7.677
3	5434395	7.674
4	5430202	7.663
5	5426720	7.665
6	5425671	7.654
Mean	5431866.0000	7.668
SD	5100.5297	0.0086
RSD%	0.0939	0.112

Table 4. Results of reproducibility of the analytical method for Ibuprofen.

Reproducibility		
Sample no	**peak area (mV/cm^2)**	**Retention time(min)**
1	5437872	7.429
2	5436336	7.405
3	5434395	7.424
4	5473828	7.453
5	5573888	7.386
6	5475833	7.408
Mean	5472025.333	7.417
SD	48733.922	0.0211
RSD%	0.890	0.284

Accuracy

The accuracy of the suggested method has been established by calculating the individual recovery and mean recovery value of IBP and the relative error. Nine prepared solutions were injected with concentrations of (80-100-120) % of the standard, which that are three replicates for each concentration. The percentage of recovery was calculated. The result was 100.48%, which is acceptable since the resulting recovery value met the acceptance requirements (a minimum of 98.0% and a maximum of 102.0%), and the relative error % was (-1.511-1.465) %. The resulting accuracy data at various levels are summarized in Table 5.

Table 5. Results of method accuracy.

Sample no	Theoretical Concentration%	peak area (mV/cm^2)	Practical Concentration%	%Recovery	Relative Error%
1	80	4407352	80.805	101.007	1.007
2	80	4406442	80.788	100.986	0.986
3	80	4405543	80.771	100.964	0.964
4	100	5441529	100.301	100.301	0.301
5	100	5442433	100.318	100.318	0.318
6	100	5345425	98.489	98.489	-1.511
7	120	6579784	121.758	101.465	1.465
8	120	6489776	120.061	100.051	0.051
9	120	6533411	120.884	100.736	0.736
% Recovery Mean				**100.48**	

Specificity

Specificity of the method can be characterized as the capacity to accurately determine the response of the examined substance without influence from the sample matrix. To determine the specificity of the method, a standard IBP was compared to a proposed formulation comprising IBP with excipients in terms of retention time, where the retention time of ibuprofen in the standard sample was 7.676 ± 0.022 min, while it was in the studied formulation sample and 7.648 ± 0.006 min. The outcomes of the specificity of the developed method are illustrated in Fig. 5, where A shows the resulting chromatogram from the injection of the ibuprofen standard solution, and B shows the resulting chromatogram from the injection of the sample containing ibuprofen with the excipients. These results imply that the formulation components had no effect on IBP analysis using this method, and the excipients had no effect on the shape of the IBP peak or retention time. As a result, the method is specific.

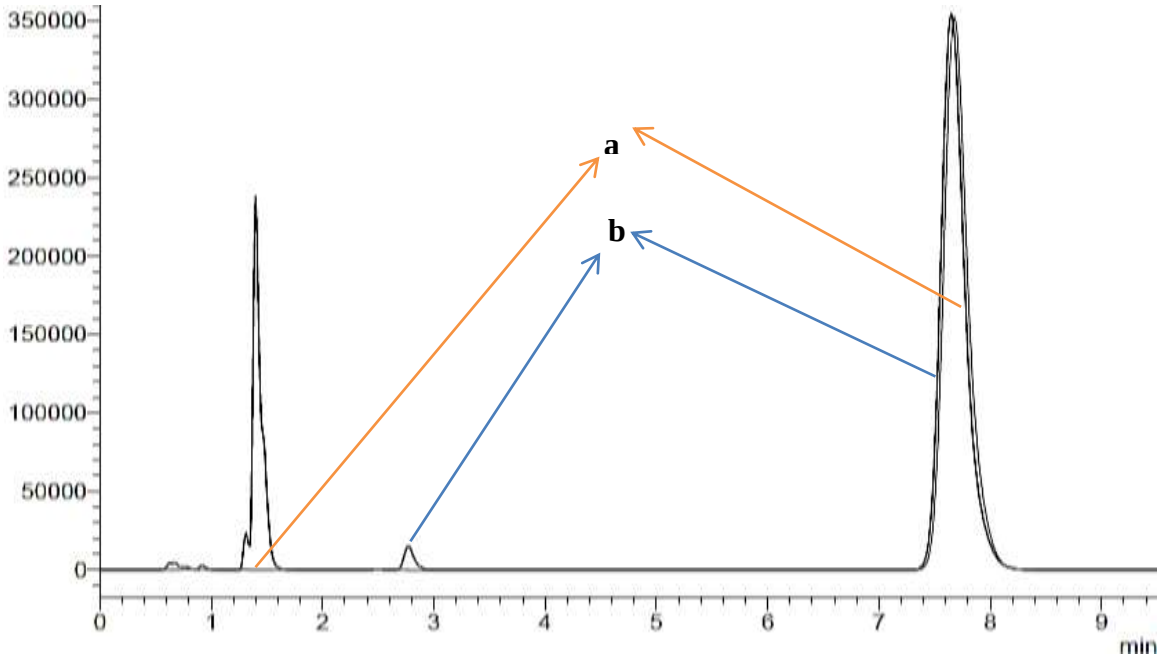

Figure 5. Chromatogram resulting from injection of ibuprofen solutions, where: a: chromatogram resulting from injection of ibuprofen standard solution, b: chromatogram resulting from injection of sample containing ibuprofen with excipients.

LOD and LOQ

The sensitivity of method was established by calculating LOD and LOQ. Depending on the value of slope = 5304751.351 and Eq.1 , LOD was estimated to be 0.036 mg/mL, while LOQ was estimated to be 0.110 mg/mL using Eq.2 . These results indicate a good sensitivity of the method.

Results of Application of the method on pharmaceutical suspension

By applying the proposed method for analyzing IBP in the different studied products, the values of recovering the amount of IBP found in the pharmaceutical preparations (100 mg/5mL) were equal to 99.80% with RSD% = 0.084%, 98.92% with RSD% = 0.109%, 100.01% with RSD% = 0.097% for A, B, C suspension respectively. Fig.6 shows the chromatograms resulting from the analysis of sample suspension A, B and C, respectively, where the same peak of ibuprofen was observed with a difference in other peaks between the suspensions, and this indicates difference in excipients used in formulating of suspensions. As a result, we found that this method can be used to quality control of IBP in its pharmaceutical form.

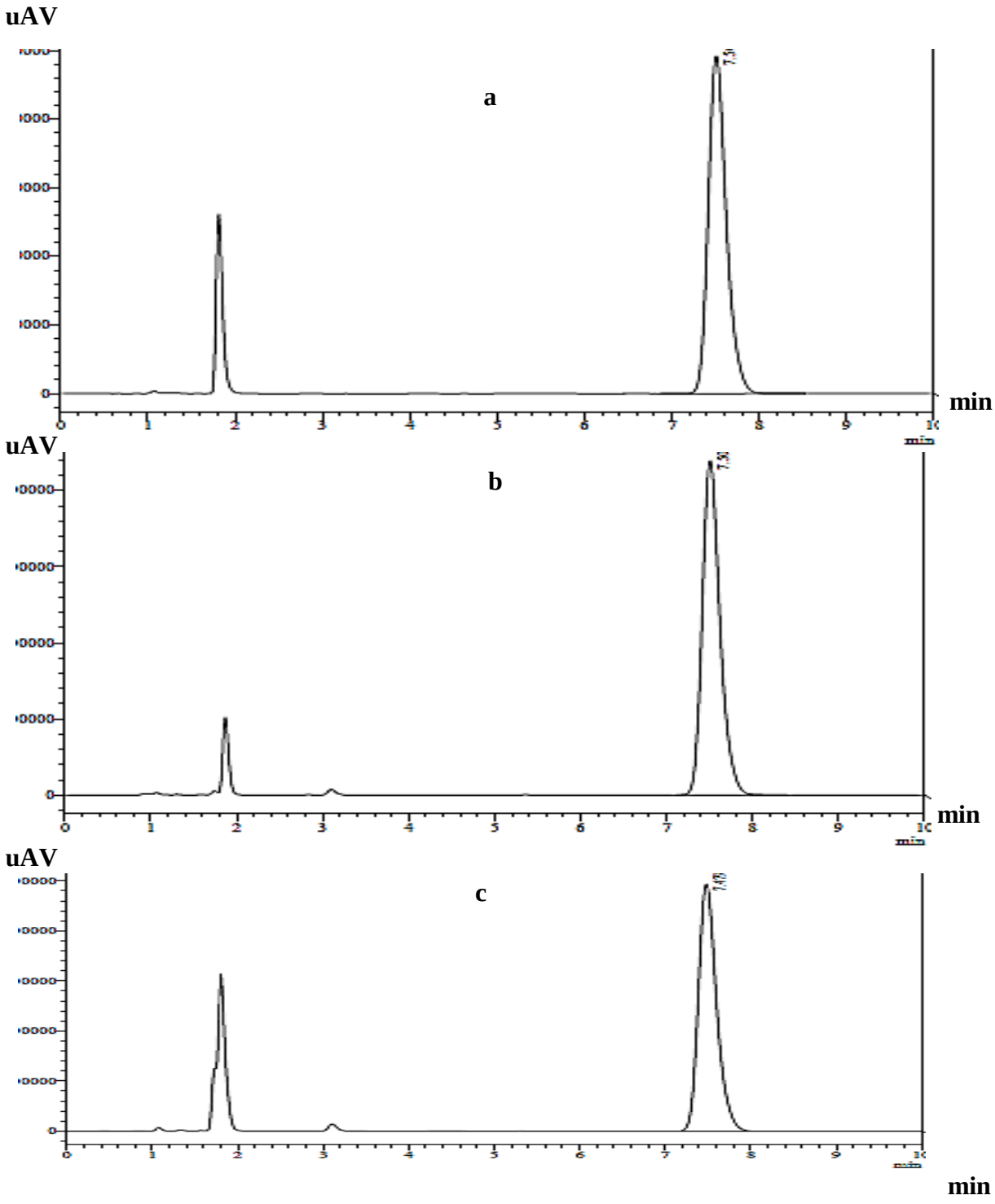

Figure 6. The chromatograms resulting from the analysis of the sample A and B and C, where, a: The chromatogram resulting from the analysis of the suspension A., b: The chromatogram resulting from the analysis of the suspension B., c: The chromatogram resulting from the analysis of the suspension C.

Conclusion:

In this study, a simple analytical method for detecting and quantifying ibuprofen in bulk drug and suspension dosage form was effectively developed and revalidated. The proposed method was shown to be extremely repeatable, accurate, linear, and precise. It is simple, dependable, reproducible, economical, and quick since the

materials and instruments utilized in this procedure are simple and do not require any sophisticated tools. It can be used in any laboratory with a basic HPLC system to analysis IBP in less retention times, allowing a large quantity of samples of ibuprofen to be analyzed. In addition, this suggested RP-HPLC method is recommended for analyzing ibuprofen in bulk drug and in pharmaceutical suspension for routine quality control.

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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 Al-Baath University.

Authors' contributions statement:

K. E. contributed to the design, analysis, interpretation, drafting, and writing of the manuscript. Y. H. contributed to the revision and proofreading the manuscript (supervisor).

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تطوير طريقة كروماتوغرافيا سائلة عالية الأداء ذات الطور العكوس بسيطة وحساسة لتقدير الإيبوبروفين في المعلقات الصيدلانية والتحقق من مصدوقيتها

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الخلاصة:

كان الهدف من هذا العمل هو تطوير طريقة سريعة ومنخفضة التكلفة لتقدير الإيبوبروفين في المعلقات الصيدلانية باستخدام الكروماتوغرافيا السائلة عالية الأداء ذات الطور العكوس، والتحقق من صحتها. تم تنفيذ الطريقة المقترحة والتحقق من مصدوقيتها وفقًا لمتطلبات المؤتمر الدولي للمواءمة (ICH). كانت المعاملات الكروماتوغرافية كالتالي: عمود أوكتيل ديسيل سيليل C18 بأبعاد (150 × 4.6) ملم، طور متحرك مكون من أسيتونيتريل مع حمض الفوسفوريك بنسبة 50 إلى 50 لكل منهما باستخدام النموذج الثابت isocratic ، معدل تدفق 1.5 مل/ دقيقة وحجم الحقنة 5 ميكرولتر، طول موجة كاشف الأشعة فوق البنفسجية 220 نانومتر. تم التحقق من صحة الطريقة وأظهرت زمن احتباس قصير لقمة الإيبوبروفين عند 7.651 دقيقة ، مع خطية على المجال المدروس من 0.4 - 1.6 ملغ/ مل (R^2 = 0.9999) ومع مضبوطية عالية [كانت نسبة الاسترداد (100.48٪)، والخطأ النسبي المئوي (-1.511- 1.465)%]، وتكرارية (RSD٪ = 0.112 لزمن الاحتباس). تم حساب حد الكشف والحد الكمي لتكون 0.036 و 0.110 ملغ/ مل على التوالي. تم تطبيق هذه الطريقة بنجاح لتقدير محتوى الإيبوبروفين في ثلاثة منتجات صيدلانية تجارية. بالنظر إلى الوقت القصير للتحليل وحد الكشف المنخفض، نوصي بهذه الطريقة للمقايسات الروتينية في مختبرات مراقبة الجودة وكطريقة جيدة لدراسات الثبات للإيبوبروفين.

الكلمات المفتاحية : تطوير، إيبوبروفين، مصداقية الطريقة، الكروماتوغرافيا السائلة عالية الأداء ذات الطور العكوس، معلّق.