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Short Communication

RAPID AND SIMPLE DETERMINATION OF IBUPROFEN AND CAFFEINE IN FIXED-DOSE COMBINATION FORMULATIONS: APPLICATION TO DISSOLUTION STUDIES

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ABSTRACT

Objective: To develop a UV-derivative spectrophotometric method with zero-crossing determinations for the simultaneous quantification of ibuprofen (IBU) and caffeine (CAF) in fixed-dose combination formulations (soft gelatin capsules). The proposed method was validated, and it was applied to determine the *in vitro* dissolution performance of IBU and CAF from a commercial formulation.

Methods: The method is based on the use of the second-derivatives of the zero-order spectra and measurement at zero-crossing wavelengths. Linearity, accuracy, precision, stability, and influence of the filter were evaluated. Dissolution profiles of IBU and CAF were obtained with the USP Apparatus 2 at 100 rpm and 900 ml of 0.1 M phosphate buffer pH 7.4 as dissolution medium. Dissolution samples were treated with the proposed UV-derivative method and results were compared with data previously published.

Results: The zero-crossing points for the determination of IBU and CAF were found at 235.6 nm and 218.8 nm, respectively. The method was linear in the range of 7.5-15 µg/ml for IBU and 5-25 µg/ml for CAF (R^2>0.999, *P<0.05). The precision and accuracy of the method were within acceptable criteria (CV<0.99% and recovery 97.97% for IBU and CV<1.76% and recovery 99.05% for CAF). Fiberglass filters were the best option to filter samples and stability of all drugs was adequate when solutions were stored at 25 °C during 24 h. Dissolution of IBU and CAF at 60 min was 99-100% with dissolution profiles of sigmoidal S-shape. Weibull function and Logistic were the best-fit models that describe the *in vitro* dissolution performance of both drugs.

Conclusion: The proposed UV-derivative method allows the simultaneous determination of IBU and CAF in fixed-dose combination formulations. The method generates reliable information that can be compared with published data. The proposed UV-derivative method is rapid and simple and can be easily adopted for routine analysis of IBU and CAF.

Keywords: Caffeine, Derivative spectroscopy, Ibuprofen, USP Apparatus 2

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Many drug products containing mixtures of drugs are manufactured as fixed-dose combination formulations. Some advantages have been identified for this kind of formulations: 1. Greater efficacy compared with higher dose monotherapy; 2. Reduced risk of adverse reactions relative to higher dose monotherapy; 3. Lower overall costs, and 4. Improve medication concordance [1]. These advantages can be seen when treating different conditions with various combinations of drugs. Fixed-dose combination formulations of ibuprofen (IBU) and caffeine (CAF) are widely available as over-the-counter products. IBU is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory, and antipyretic properties [2]. Some authors have studied the effect of CAF on pain management [3-5]. CAF is an extremely common drug in commercial products, and it occurs in a wide range of cold remedies, analgesics and other types of medicines. CAF is clinically safe, and it has good pH-independent aqueous solubility in the physiological pH range (~50 mg/ml) [6]. Chemical structures of IBU and CAF are shown in fig. 1.

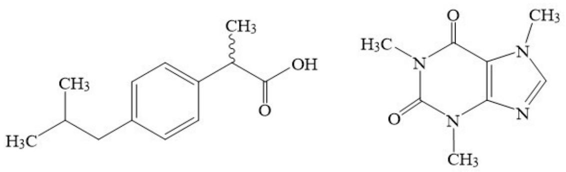

Fig. 1: Chemical structures of ibuprofen (left) and caffeine (right)

A review of analgesic effect of IBU and CAF mixture was previously reported [7]. The use of this combination in preclinical studies [8, 9], the effectiveness of a single dose of IBU/CAF tablets in postoperative pain [10] and especially in molar surgeries has been widely documented [10-14].

According to Biopharmaceutics Classification System (BCS) criteria drugs with low solubility and high permeability are classified as class II drugs [15]. Several authors have classified IBU as a class II drug [16, 17]. By the available scientific information, formulations with IBU as the only active pharmaceutical ingredient (API), are candidates to waiver *in vivo* studies. A biowaiver monograph for immediate-release solid oral dosage forms containing IBU has been published [2]. However, only fixed-dose combinations containing BCS class I, or class III, or a combination of class I and class III may be candidates for a biowaiver [18] so this approach for IBU/CAF drug products, is not applicable. Official dissolution test for IBU suspensions and tablets are described in the United States Pharmacopeia (USP) [19]. Both methods use the USP Apparatus 2 at 50 rpm and 900 ml of phosphate buffer pH 7.2 as dissolution medium. To date, no official dissolution test for IBU/CAF fixed-dose combination formulations is available [19].

Several authors have studied the simultaneous determination of CAF combined with some NSAIDs in pharmaceutical formulations [20, 21]. The quantification of the ternary mixture of acetaminophen (ACE), IBU, and CAF in solid dosage forms using analytical methods as UV and HPLC [22, 23] as well as voltammetric determination [24] have been previously described. Specifically, for IBU/CAF mixture, analytical methods with gas chromatography in pharmaceutical dosage forms [25], Raman spectroscopy in water samples [26] and fluorescence in urine samples [27] were recently reported. However, in a complete review of spectrophotometric methods for determination of some mixtures the combination of IBU and CAF is not included [28].

In the present study, a rapid and simple UV-derivative method with measurements at zero-crossing points is proposed for determination of IBU and CAF in fixed-dose combination formulations (soft gelatin capsules). The method was applied in dissolution studies using USP Apparatus 2 (paddle) at 100 rpm and 0.1 M phosphate buffer pH 7.4 as dissolution medium. The objective is to have a reliable and easy method to determine IBU and CAF using the minimum possible analytical resources. Results were compared with published data.

IBU and CAF standards were purchased from Sigma-Aldrich Co. (St. Louis MO, USA). Sodium phosphate monobasic and dibasic crystals and methanol HPLC grade were purchased from J. T. Baker-Mexico (Xalostoc, Mexico). The fixed-dose combination formulation of IBU and CAF (200/65-mg, respectively) used was Advil Lift® capsules (Procaps S. A., Barranquilla Colombia).

For UV derivative analysis, a double beam UV/Vis spectrophotometer (Perkin Elmer Lambda 35, Waltham MA, USA) with 1-cm quartz cells was used. The operating conditions were second-derivative (^{2}D) mode with scan speed of 240 nm/min, slit width 2.0 nm and sampling interval 1.0 nm.

The preparation of standard solutions of IBU and CAF were as follows: 10 mg of each drug were separately added to 10 ml volumetric flasks. A volume of 5 ml of methanol was added to each one then, flasks were sonicated during 10 min. Later, both flasks were diluted to the mark with 0.1 M phosphate buffer pH 7.4. From both stock solutions, five solutions of IBU (7.5-15 µg/ml) and five solutions of CAF (5-25 µg/ml) in 0.1 M phosphate buffer pH 7.4 were prepared. Then, zero-order spectra of all solutions from 200 to 350 nm, using 1-cm quartz cells, were recorded and stored. To quantify IBU and CAF, the stored spectra of the standard calibration curves were used to calculate the ^{2}D. To quantify IBU and CAF in dissolution samples, the zero-order spectra of filtered solutions at adequate concentrations were recorded and stored. Subsequently, the ^{2}D spectra of IBU and CAF, as well as data of standard calibration curves, were used to calculate the percent dissolved of each drug at previously established sampling times.

To test linearity, two standard calibration curves of IBU and CAF were plotted. Data were fitted by linear regression analysis and the correlation coefficients and regression analysis of variance (ANOVA) were calculated. The 95% Confidence Interval ($CI_{95\%}$) for the intercept of each mean standard calibration curve was calculated. Precision was demonstrated with the calculation of percent of coefficient of variation (%CV): [(standard deviation/mean) × 100] of response factor. Response factor represents the proportionality of response *vs.* drug concentration. A CV≤2% was considered as a good criterion. Accuracy and precision were evaluated with the preparation of three synthetic mixtures of IBU and CAF with concentrations within standard calibration curves range of each drug. Then, four samples of each solution and a standard calibration curve of each drug were analyzed with the proposed UV-derivative method. Accuracy was validated by recovery data and precision with the calculation of %CV. Added *vs.* recovered concentrations were plotted and linear regression analysis were calculated. The $CI_{95\%}$ of slopes and intercepts, as well as %CV at each concentration level, were estimated. Drug retention by some kinds of filters was evaluated by response of IBU and CAF before and after a synthetic mixture of both drugs was filtered (10 µg/ml of IBU and 20 µg/ml of CAF). Nitrocellulose and fiberglass filters were tested. Percent of absolute difference (%AD): [((initial response–final response)/initial response) × 100] was calculated with 10 samples. The IBU and CAF stability was evaluated by stored a synthetic mixture (13 µg/ml of IBU and 20 µg/ml of CAF) at 4 and 25 °C during 24 and 72 h. The %AD was calculated by triplicate at each temperature and sampling time.

Dissolution profiles of IBU/CAF capsules were obtained with a USP Apparatus 2 (paddle) (Sotax AT-7 Smart, Switzerland) at 100 rpm and 900 ml of 0.1 M phosphate buffer pH 7.4 (37.0±0.5 °C). Each dissolution profile was calculated with 12 replicates. After addition of capsules, 5 ml of filtered dissolution sample was withdrawn at 10, 25, 30, 45, and 60 min. All samples were diluted at adequate concentrations and they were analyzed by the proposed UV-derivative method. Dissolved drug at 60 min (Q_{60}) was used for comparative purposes. In order to describe the *in vitro* dissolution performance of IBU/CAF from commercial capsules mean dissolution time (MDT) and dissolution efficiency (DE) were calculated. Both model-independent parameters have been suggested as suitable parameters to compare dissolution profiles [29, 30] and to establish an *in vitro*/*in vivo* correlation [31]. Additionally, dissolution data of both drugs were fitted by several mathematical models commonly used in dissolution studies as Weibull, logistic, Gompertz and Probit. Equations are shown in table 1. Best-fit model was the one that presented highest $R^2_{adjusted}$ and lowest Akaike Information Criterion (AIC) [32]. DDSolver add-in program was used to calculate MDT and DE and fit dissolution data [33].

Table 1: Mathematical models used to fit dissolution data of IBU and CAF

Model	Equation
Weibull	$F = F_{max} \cdot \left(1 - e^{-\frac{t^{\beta}}{\alpha}}\right)$
Logistic	$F = F_{max} \cdot \frac{e^{\alpha+\beta \cdot log(t)}}{1+e^{\alpha+\beta \cdot log(t)}}$
Gompertz	$F = F_{max} \cdot e^{-\beta \cdot e^{-k \cdot t}}$
Probit	$F = 100 \cdot \phi[\alpha + \beta \cdot log(t)]$

IBU: ibuprofen. CAF: caffeine

The zero-order spectra of 0.1 M phosphate buffer pH 7.4 solutions of IBU at 10 µg/ml, CAF at 15 µg/ml and a synthetic mixture of both drugs (MIX) at same concentrations are depicted in fig. 2A. The zero-order spectrum of MIX solution demonstrated a marked overlapping so that the direct and simultaneous determination of IBU and CAF was not possible. The ^{2}D of zero-order spectra of five standard solutions of IBU (7.5-15 µg/ml) and five solutions of CAF (5-25 µg/ml), as well as MIX solution (10 µg/ml of IBU and 15 µg/ml of CAF), are shown in fig. 2B. The zero-crossing points for determination of IBU and CAF were identified at 235.6 and 218.8 nm, respectively. At these wavelengths, all analytical signals were proportional to the concentrations of drugs and as can be seen, no interference of each drug was found.

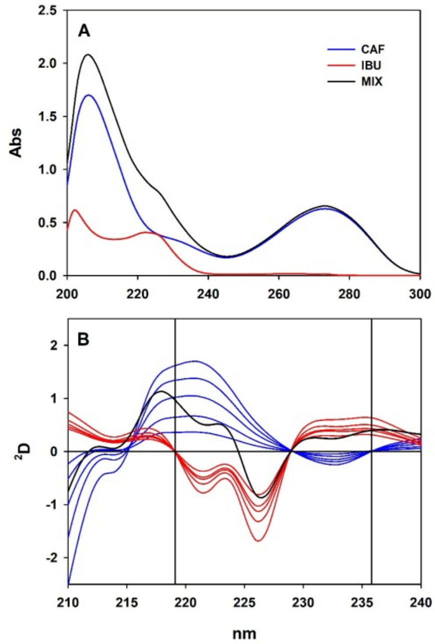

Fig. 2: (A) Zero-order spectra of a solution of ibuprofen (IBU) at 10 µg/ml, caffeine (CAF) at 15 µg/ml and a synthetic mixture of both drugs (MIX) at same concentrations. (B) Second-derivative (^{2}D) of standard calibration curves and MIX solution. Vertical lines show the zero-crossing points used to quantify IBU (235.6 nm) and CAF (218.8 nm)

Of each drug, two standard solutions were prepared, and mean linear regression equations were as follows: y=0.0502x–0.0154 for IBU and y=0.0797x+0.0138 for CAF. All standard calibration curves were significant (R^2>0.999, *P<0.05). Plots are shown in fig. 3A and fig. 3B. The

$CI_{95\%}$ calculated for intercept was-0.044 to 0.013 for IBU and-0.014 to 0.041 for CAF. The %CV of response factor was 1.75% for IBU and 1.86% for CAF. The linear regression equations calculated to test accuracy were as follows: y=1.0291x–0.5758 for IBU and y=1.053x–0.7383 for CAF. All linear regressions were significant (R^2>0.99, *P<0.05). Plots are shown in fig. 3C and fig. 3D. The $CI_{95\%}$ for slopes and intercepts, respectively, were as follows: 0.56 to 1.49 and −6.10 to 4.95 for IBU and 0.66 to 1.44 and −5.91 to 4.43 for CAF. The %CV of recovery data were 0.58 to 0.99% for IBU and 0.34 to 1.76% for CAF. Results shown a good accuracy and precision of the proposed UV-derivative method.

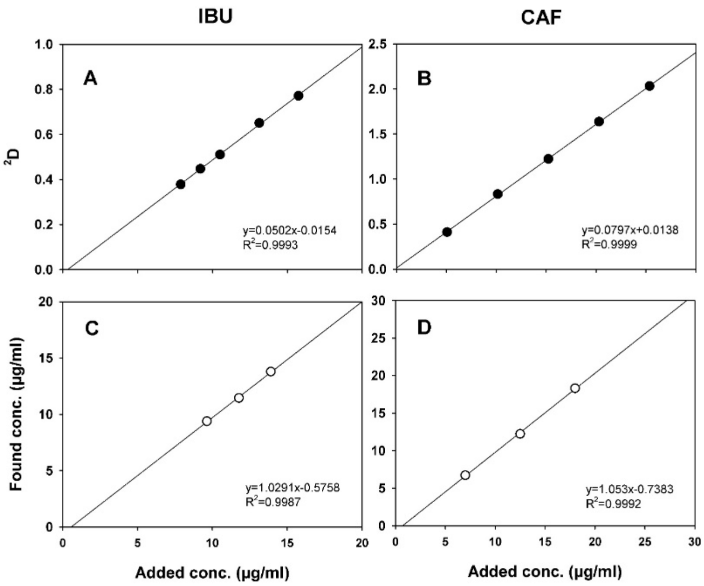

Fig. 3: (A) and (B) Standard calibration curves (mean values, n=2). (C) and (D) Synthetic mixtures (mean values, n=4) of ibuprofen (IBU) and caffeine (CAF). All linear regressions were significant (*P<0.05)

The lowest values of %AD to test the influence of the filter were 0.46% for IBU and 4.6% for CAF, both data were calculated with fiberglass filters so, this kind of filter was used in dissolution studies. Values of %AD to test the stability of IBU at 25 °C and 24 and 72 h were-3.25 and-4.74%, respectively. Data of CAF at same conditions were 0.40 and 0.88%. Values of %AD of IBU at 4 °C and at 24 and 72 h were-5.03 and-7.05%, respectively. Data of CAF at same conditions were-0.6 and-0.63%. Results suggest better stability of a synthetic mixture of IBU and CAF at 25 °C for 24 h.

Dissolution profiles of IBU and CAF from fixed-dose combination formulation are depicted in fig. 4. The Q_{60}, MDT, and DE values are shown in table 2.

The *in vitro* dissolution performance of IBU and CAF shown a sigmoidal S-shape with a complete drug release at 60 min (100%). Application of the UV-derivative method showed that excipients do not affect the accuracy of our results since recovery (expressed as Q_{60} data) is similar than results obtained with gas chromatography and HPLC methods applied at IBU/CAF fixed-dose combination formulations (99-100% for both drugs) [25].

The $R^2_{adjusted}$ and AIC values as a result of adjusting IBU and CAF dissolution data by several mathematical models are shown in table 3. Weibull function was the best-fit model for IBU data and the Logistic equation for CAF data.

Weibull and Logistic models cannot describe drug release kinetics, but they can describe the curve in terms of applicable parameters [34]. The shape parameter β characterizes the dissolution profile as exponential (β=1); as sigmoid S-shaped, with upward curvature followed by a turning point (β>1); or as parabolic, with a steeper initial slope that is consistent with the exponential (β<1) [35]. In the present study, mean β values±standard deviation of IBU (Weibull) and CAF (Logistic) were 2.79±0.37 and 10.08±1.93, respectively, and since β values were>1 sigmoidal profile for both drugs was considered. Similar results have been reported by several authors wherein a dissolution study of IBU suspensions (USP Apparatus 2 and 4 and phosphate buffer pH 7.2) two formulations were well fitted by Weibull function ($R^2_{adjusted}$>0.99) [36]. Another dissolution study but with ACE/IBU fixed-dose combination formulations (USP Apparatus 2 and 4 and 0.1 M phosphate buffer pH 7.4) reported a best-fit with Weibull distribution ($R^2_{adjusted}$>0.999) for both drugs [37]. The fit of dissolution data to the Weibull function and Logistic model emphasized the S-shape or sigmoidal dissolution profiles [34].

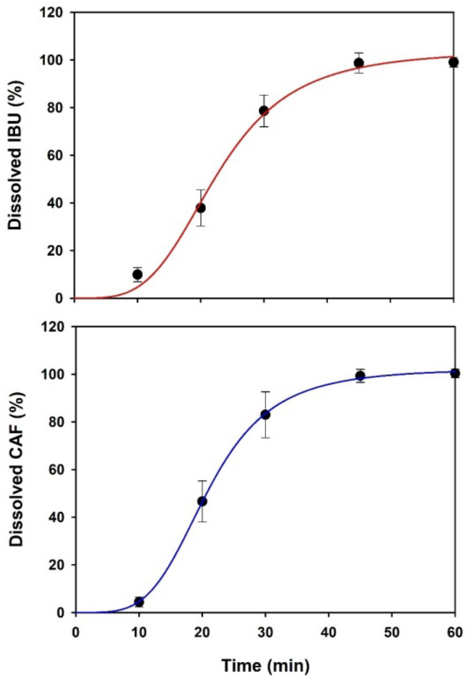

Fig. 4: Dissolution profiles of ibuprofen (IBU) and caffeine (CAF) obtained with USP Apparatus 2 at 100 rpm and 900 ml of 0.1 M phosphate buffer pH 7.4 as dissolution medium. Mean value±standard deviation, n=12

Table 2: Model-independent parameters of IBU and CAF

Drug	Q_{60} (%)	MDT (min)	DE (%)
IBU	99.05±0.58	22.81±0.52	61.39±0.89
CAF	100.37±0.72	22.23±0.72	63.17±1.15

Mean value±standard error medium, n=12. IBU: ibuprofen. CAF: caffeine. Q_{60}: dissolved drug at 30 min. MDT: mean dissolution time. DE: dissolution efficiency

Table 3: Criteria used to find the best-fit model of IBU and CAF dissolution data

Drug	Weibull	Logistic	Gompertz	Probit
$R^2_{adjusted}$				
IBU	0.9912	0.9819	0.9838	0.9826
CAF	0.9937	0.9964	0.9963	0.9953
AIC				
IBU	21.65	25.10	24.44	25.10
CAF	20.11	14.88	13.33	16.56

Mean value±standard error medium, n=12. IBU: ibuprofen. CAF: caffeine

On the other hand, the *in vitro* dissolution performance of CAF from fixed-dose formulations has been previously reported. ACE/CAF tablets were tested with USP Apparatus 1 at 100 rpm and 900 ml of fat-rich media as dissolution medium. Under these conditions more than 80% of dissolved CAF at 20 min was found [6]. CAF in a ternary mixture of drugs (tablets) was dissolved with USP Apparatus 1 at 100 rpm and 900 ml of 0.1 N HCl. More than 80% of dissolved CAF at 20 min was found [38]. In our *in vitro* dissolution study, more than 80% of dissolved CAF was found but at 30 min (82.99±9.63%, mean value±standard deviation). As the dissolution profile of CAF shown a sigmoidal S-shape it is not possible to find 80% of dissolved drug at 20 min but 10 min latter this dissolution extent was achieved. Additionally, CAF as only API manufactured in three different hypromellose (HPMC)-based controlled release tablets were tested with USP Apparatus 3 (10 and 15 dpm), water and biorelevant media (fed and fasted) [39]. Dissolution data were well fitted by the Weibull function (R^2>0.98) and under certain conditions shape parameter *b* was>1. In that study no other mathematical model to fit dissolution data was considered however and as previously stated, Weibull distribution emphasized the S-shape or sigmoidal dissolution profiles.

The proposed UV-derivative method was an analytical procedure successfully used to simultaneously identify IBU and CAF in fixed-dose combination formulations. This kind of methods avoid the use of toxic solvents such as those used by HPLC methods and expensive laboratory equipment requiring specialized maintenance. The proposed method is an analytical procedure that not needing any additional mathematical calculations and can be easily adopted for routine analysis of IBU/CAF soft gelatin capsules.

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Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLIC OF INTERESTS

Declared none

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