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Original Article

SIMULTANEOUS QUANTIFICATION OF ACETYLSALICYLIC ACID AND CAFFEINE IN TABLETS BY FIRST-ORDER DERIVATIVE SPECTROSCOPY

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ABSTRACT

Objective: To develop an apply a new and easy UV-derivative method for the simultaneous quantification of acetylsalicylic acid (ASA) and caffeine (CAF) in commercial tablets. Derivative spectroscopy is an analytical methodology used to identify drugs in a mixture of two or more compounds without use of toxic dissolvents that are involved in chromatographic determinations.

Methods: Standard solutions of ASA (40-120 µg/ml) and CAF (5-25 µg/ml) were prepared with 0.1 M phosphate buffer pH 7.4. The zero-order spectra were determined from 200-300 nm. The method was validated according to International Conference on Harmonization (ICH) guidelines. An USP Apparatus 2 at 75 rpm with 900 ml of 0.1 M phosphate buffer pH 7.4 was used. For each drug, common dissolution data as the amount of drug released at 60 min (Q_{60}), mean dissolution time (MDT), dissolution efficiency (DE), $t_{50\%}$ and $t_{85\%}$ were calculated.

Results: ASA was identified at 245 nm and CAF at 295 nm in the first-derivative mode. The method was linear (R^2>0.99, *P<0.05). The precision and accuracy of the method were within acceptable limits. Q_{60}, MDT, DE, $t_{50\%}$, and $t_{85\%}$ values for ASA were 102.09%, 8.18 min, 88.15%, 2.91 min, and 11.98 min, respectively. Same parameters for CAF were 99.17%, 5.21 min, 90.54%, 1.09 min, and 5.70 min, respectively.

Conclusion: The proposed UV-derivative method is rapid and simple and can be easily adopted to determine the *in vitro* release curves of ASA and CAF from commercial tablets. The method generates reliable information that can be compared with published data.

Keywords: Acetylsalicylic acid, Caffeine, Derivative spectroscopy, *In vitro* release curves

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INTRODUCTION

Drug products with the combination of acetylsalicylic acid (ASA) or other analgesic drugs and caffeine (CAF) are widely available all around the world. The study of interactions of these compounds and excipients that can seriously affect some technological properties during manufacturing as well as the solubility, dissolution rate and bioavailability, is still investigated by several authors [1, 2]. ASA is a commonly drug used in the treatment of fever, headache and cardiovascular illness [3]. CAF is clinically safe and its effect on pain management has been reported by several authors [4, 5]. Molecular structures of ASA and CAF are shown in fig. 1.

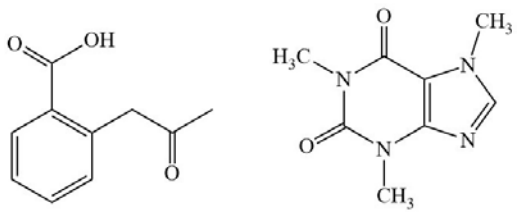

Fig. 1: Molecular structures of ASA (left) and CAF (right)

According to Biopharmaceutical Classification System (BCS) ASA is a class I drug (high solubility/high permeability)[6] while CAF has good pH-independent aqueous solubility in the physiological pH range (~50 mg/ml) [7]. Based on previously published scientific information, a BCS-based biowaiver procedure can be recommended for approval of new formulations of solid oral dosage forms containing ASA as the only active pharmaceutical ingredient [6]. On the other hand, only fixed-dose combinations formulations containing BCS class I, or class III, or a combination of class I and class III may be candidates for a biowaiver [8] so this approach is not applicable for ASA/CAF tablets as to date, CAF has not been classified.

Official dissolution test for ASA tablets is described in the United States Pharmacopeia (USP). The method indicates the use of the USP Apparatus 1 (basket) at 50 rpm and 1000 ml of 0.05 M acetate buffer pH 4.5 as a dissolution medium. Under these conditions, not less than 80% of the drug should be dissolved in 30 min [9]; however, no official dissolution test for ASA/CAF tablets is still available.

Chromatographic analysis for composed mixtures of ASA and antihypertensive, antiplatelet or antithrombotic agents, as well as CAF combined with some non-steroidal anti-inflammatory drugs (NSAIDs), have been developed by several authors [10-12]. Specifically, for ASA and CAF mixture in pharmaceutical formulations, spectrofluorometric [13] and electrochemical [3, 14] determinations have been published. Electrochemical analysis has also been proposed for simultaneous quantification of ASA and CAF in human urine samples [15]. Some techniques have been suggested for the treatment of spectrophotometric data from spectra composed of unresolved bands [16-18]; nevertheless, a UV-derivative method for simultaneous identification of ASA and CAF is not included.

In the present study, a rapid and simple UV-derivative method with measurements at zero-crossing points is proposed for the determination of ASA and CAF in a commercial formulation (immediate-release tablets). To verify the applicability of this procedure, the method was used to determine the *in vitro* release curve of each drug using the USP Apparatus 2 (paddle) at 75 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 ASA and CAF using limited analytical resources. Results were compared with published data.

MATERIALS AND METHODS

Chemicals and instruments

ASA and CAF standards were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). Sodium phosphate monobasic and dibasic crystals as well as methanol AR grade, were purchased from J. T. Baker-Mexico (Xalostoc, Mexico). The fixed-dose combination formulation

containing ASA and CAF (500/30-mg, respectively) was Cafiaspirina® tablets (Bayer de México S. A de C. V.). Mexican health authorities have established this commercial brand as a reference drug product for *in vitro* and *in vivo* studies [19].

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 first-derivative (^{1}D) mode with scan speed of 240 nm/min, slit width 2.0 nm and sampling interval 1.0 nm. *In vitro* release curves of ASA and CAF were determined in an USP Apparatus 2 (paddle) at 75 rpm (Sotax AT-7 Smart, Switzerland) with 900 ml of 0.1 M phosphate buffer pH 7.4 (37.0±0.5 °C) as dissolution medium. Samples of 5 ml were withdrawn at 10-, 20-, 30-, 45-, and 60-min. All samples were diluted at adequate concentrations, and they were analyzed by the proposed UV-derivative method.

Content uniformity and assay

Content uniformity and assay tests were performed according to the procedures described in the USP [9].

Standard calibration curves of ASA and CAF

The preparation of the standard calibration curves of ASA and CAF were as follows: 10 mg of each drug were separately added to 10 ml volumetric flasks. Then, a volume of 5 ml of methanol was added to each one and 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 ASA (40-120 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 ASA and CAF, the stored spectra of the standard calibration curves were used to calculate the ^{1}D. To quantify ASA and CAF in dissolution samples, the zero-order spectra of filtered solutions at adequate concentrations were recorded and stored. Subsequently, the ^{1}D spectra of ASA and CAF, as well as data of standard calibration curves, were used to calculate the dissolved amount of each drug at previously established sampling times.

Analytical method validation

The proposed UV derivative method was validated according to the International Conference on Harmonization (ICH) guidelines [20]. System linearity, accuracy, precision, and stability were determined.

Linearity

Two series of standard calibration curves of ASA and CAF in 0.1 M phosphate buffer pH 7.4 were determined. Then, ^{1}D response at certain wavelength was recorded. Data obtained were fitted by linear regression analysis and the coefficients of regression and regression analysis of variance (ANOVA) were calculated. The response *vs.* ASA and CAF concentration proportionality was demonstrated by calculating the percentage relative standard deviation (RSD) of the response factor across the calibration curve range as follows:

$$\text{RSD} = \left(\frac{\text{standard deviation}}{\text{mean}}\right) \times 100 \text{ .... Eq. 1}$$

Accuracy and precision

In order to verify the accuracy and precision of the proposed UV-derivative method, the standard addition method was used, thus, matrix effects can be easily removed. This procedure can be used for resolving binary mixtures in complex samples with unknown matrices. Twenty tablets were accurately weighed and crushed in a mortar; then, quantities of powder of ASA and CAF tablets plus a quantity of ASA or CAF standard (10 mg) to finally give the equivalent of 80, 100, and 120% of the dose of each drug, were separately dissolved in 900 ml of 0.1 M phosphate buffer pH 7.4 at 37.0±0.5 °C. For this purpose, the USP Apparatus 2 (paddle) at 75 rpm was used. At 60 min, the amounts of dissolved ASA and CAF were calculated with reference to a standard calibration curve prepared on the day of the experiment. Each determination was performed in triplicate. The percentage relative error (RE) was taken as a measure of the accuracy and the RSD as a measure of precision. Experiments were carried out in three consecutive days. RE was calculated as follows:

$$\text{RE} = \left(\frac{\text{found}-\text{added}}{\text{added}}\right) \times 100 \text{ ..... Eq. 2}$$

Stability

Stability of analytical solutions was evaluated by analyzing two solutions of ASA (50 and 100 µg/ml) and two solutions of CAF (8 and 22 µg/ml) in 0.1 M phosphate buffer pH 7.4. These solutions were analyzed at 0 h at 25 °C (zero time) and at 24 and 48 h after stored at 4 and 25 °C. At 24, and 48 h (at each temperature) the percentage of absolute difference (AD) recovered of ASA and CAF was calculated as follows:

$$\text{AD} = \left(\frac{\text{initial}-\text{final}}{\text{initial}}\right) \times 100 \text{ .... Eq. 3}$$

Data analysis

In order to describe the *in vitro* release performance of ASA and CAF from commercial tablets dissolved drug at 60 min (Q_{60}), mean dissolution time (MDT) and dissolution efficiency (DE) were calculated. MDT and DE have been suggested as suitable parameters to compare *in vitro* release curves [21, 22] and they also can be used to establish a meaningful *in vitro*/*in vivo* correlation [23]. To get the values of MDT and DE the DDSolver add-in program was used [24]. Additionally, *in vitro* release data of ASA and CAF were fitted to the hyperbola equation:

$$y = \frac{ax}{b+x} \text{ ..... Eq. 4}$$

For this activity, Sigma Plot software (Version 11.0) was used. With *a* and *b* parameters, values of $t_{50\%}$ and $t_{85\%}$ were calculated.

RESULTS AND DISCUSSION

Content uniformity and assay

The reference drug product used met the content uniformity and pharmacopoeial assay criteria. The percentages of ASA and CAF on the content uniformity test ranged from 85 to 115% and the assay test was between 90 and 110%. Results are shown in table 1.

Table 1: Content uniformity and assay results of acetylsalicylic acid (ASA) and caffeine (CAF)

Drug	Content uniformity (%min–%max)	Assay (%)
ASA	98.25–98.67	98.41±0.15
CAF	99.79–105.05	102.61±2.10

Data are expressed as mean±standard deviation (n=10).

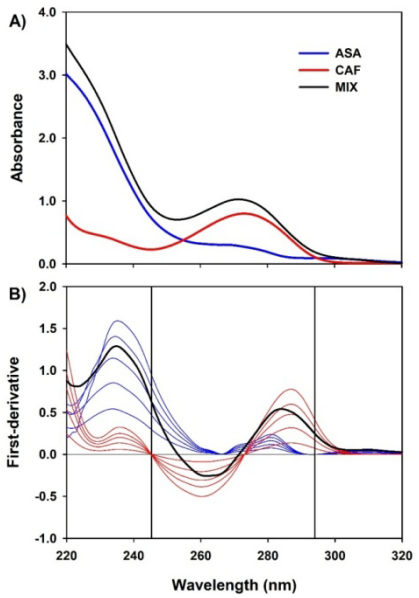

Fig. 2: (A) Zero-order spectra of a solution of acetylsalicylic acid (ASA) at 80 µg/ml, caffeine (CAF) at 15 µg/ml and a synthetic mixture of both drugs (MIX) at same concentrations. (B) First derivative of standard and MIX solutions. Vertical lines show

the zero-crossing points used to quantify ASA (245 nm) and CAF (295 nm)

Absorption spectra

The zero-order spectra of ASA at 80 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 quantification of ASA and CAF was not possible. The ^{1}D of zero-order spectra of five standard solutions of ASA (40-120 µg/ml) and five solutions of CAF (5-25 µg/ml), as well as the MIX solution (80 µg/ml of ASA and 15 µg/ml of CAF), are shown in fig. 2B. The zero-crossing points for determination of ASA and CAF were identified at 245 and 295 nm, respectively. At these wavelengths, all analytical signals were proportional to the drug concentrations and as can be seen, no simultaneous interference was found.

Method validation

Linearity

The mean regression equation from two standard calibration curves of ASA and CAF are shown in fig. 3. Both linear regressions were significant (R^2=0.999; *P<0.05). The RSD value of the response factor for ASA and CAF ranges was<3%.

Accuracy and precision

In order to prove the accuracy and precision of the proposed UV-derivative method, an analysis of some percentage of the dose of each drug was carried out for three days (n=3/d). The within-day and between-day precision and accuracy were calculated, and the results are shown in table 2. The RSD obtained was in the range of 0.37–2.57% and the RE was lower than 2.90% for both drugs in all selected dose percentages, which indicates good accuracy and precision of the method.

Stability

The stability of both drugs in 0.1 M phosphate buffer pH 7.4 was assessed with the analysis of two solutions of ASA and two solutions of CAF at different times. Absolute difference at 24 and 48 h are shown in table 3. As can be seen in table 3, ASA and CAF solutions were less stable at 25 °C.

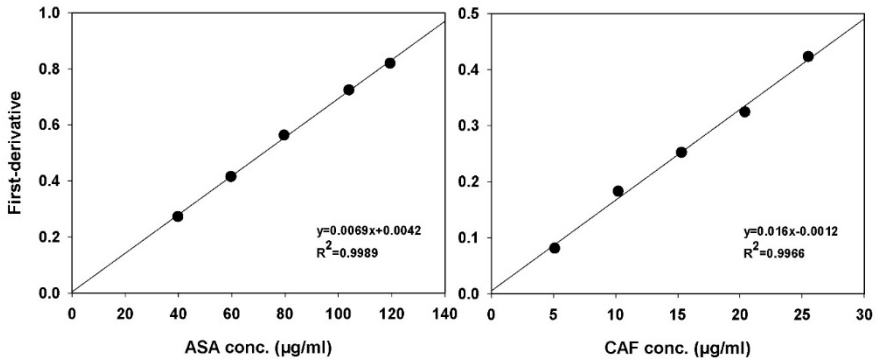

Fig. 3: Linearity of standard calibration curves of acetylsalicylic acid (ASA) and caffeine (CAF) prepared in 0.1 M phosphate buffer pH 7.4. mean data, n=2

Table 2: Accuracy and precision data for simultaneous quantification of acetylsalicylic acid (ASA) and caffeine (CAF) by the proposed UV-derivative method

		Within-day			Between-day		
Drug/dose (mg)	**Added (mg)**	**Found (mg)**	**RSD (%)**	**RE (%)**	**Found (mg)**	**RSD (%)**	**RE (%)**
ASA/500	400.00	395.45±2.77	0.70	-0.89	400.44±10.30	2.57	0.11
	500.00	503.03±4.36	0.87	0.61	502.25±6.19	1.23	0.45
	600.00	599.37±9.88	1.64	-0.10	602.18±9.95	1.65	0.36
CAF/30	24.00	24.51±0.26	1.07	2.10	24.39±0.49	2.02	1.61
	30.00	30.69±0.11	0.37	2.30	30.86±0.17	0.55	2.89
	36.00	36.06±0.41	1.15	0.21	36.12±0.34	0.94	0.33

Data are expressed as mean±standard deviation (within-day n=3; between-day n=9).

Table 3: Absolute difference (%) respect zero time to evaluate stability at 4 and 25 °C of acetylsalicylic acid (ASA) and caffeine (CAF) in 0.1 M phosphate buffer pH 7.4

Drug	**°C**	**Conc. (µg/ml)**	**24 h**	**48 h**
ASA	4	50.0	-7.61	-13.96
		100.0	-8.94	-16.94
	25	50.0	-39.55	-51.24
		100.0	-50.45	-80.85
CAF	4	8.0	2.85	5.37
		22.0	3.10	5.94
	25	8.0	18.02	26.87
		22.0	18.76	32.41

Data are expressed as mean (n=5).

Results indicate that the proposed UV-derivative method, for simultaneous quantification of ASA and CAF in tablets is linear, accurate, and precise. According to complementary ICH guideline [20], the limit of detection and limit of quantitation are characteristics not normally evaluated in dissolutions assays. For both drugs, a lack of linearity, accuracy, and precision was found at concentrations out of the proposed ranges of the standard calibration curves.

In vitro release curves of ASA and CAF are shown in fig. 4. The Q_{60}, MDT, DE, $t_{50\%}$, and $t_{85\%}$ values are shown in table 4.

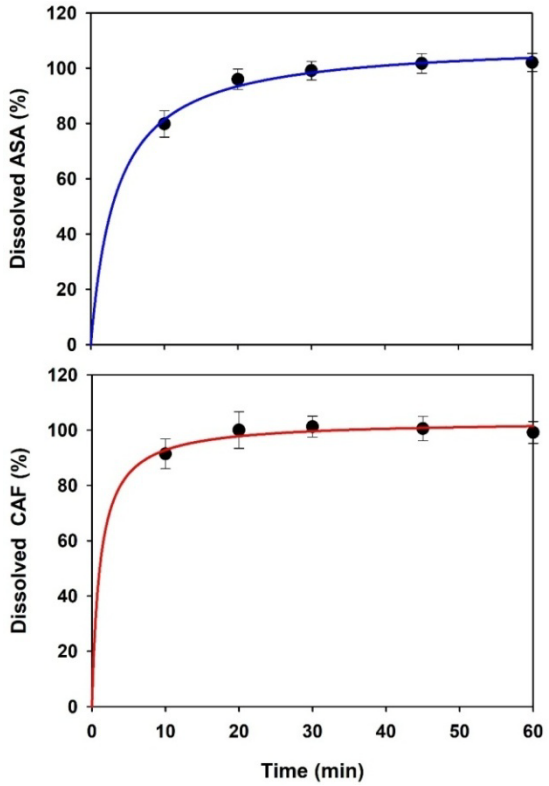

Fig. 4: *In vitro* release curves of acetylsalicylic acid (ASA) and caffeine (CAF) obtained with the USP Apparatus 2 at 75 rpm and 900 ml of 0.1 M phosphate buffer pH 7.4. Mean value±standard deviation, n=12

Table 4: Model-independent and model-dependent parameters of ASA and CAF

Drug	Q_{60} (%)	MDT (min)	DE (%)	$t_{50\%}$ (min)†	$t_{85\%}$ (min)†
ASA	102.09±0.94	8.18±0.33	88.15±0.70	2.91±0.22	11.98±0.72
CAF	99.17±1.15	5.21±0.39	90.54±1.11	1.09±0.15	5.70±0.97

Mean value±standard error medium, n=12. Q_{60}: dissolved drug at 60 min. MDT: mean dissolution time. DE: dissolution efficiency. †: derived data from the hyperbola adjustment.

The *in vitro* release performance of ASA and CAF from commercial tablets shown a complete drugs release at 60 min (100%). Application of the UV-derivative method showed that excipients do not affect the accuracy of results since recovery (expressed as Q_{60} data) is equivalent to the dose indicated on the label. An electrochemical method applied to analysis of ASA/CAF tablets reported 101.99 and 103.96% of the detected drug, respectively, with RE values less than 3.96% [15].

A dissolution study of ASA and CAF formulations combined with phenacetin has been previously published [25]. Tablets of two different sources were tested with the USP basket apparatus at 100 rpm and 1000 ml of 0.1 M HCl as dissolution medium. More than 80% of ASA and 100% of CAF were dissolved at 30 min. In our study and at the same time, but with different *in vitro* conditions, the complete dose of both drugs was also released. On the other hand, acetaminophen/CAF tablets were tested with the USP basket apparatus at 100 rpm and 900 ml of fat-rich media as dissolution medium. Under these conditions, more than 80% of CAF was released at 20 min [7]. Similar results were reported when 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 [25].

Due no UV-derivative spectrophotometric method for the simultaneous quantification of ASA and CAF in commercial formulations has been reported, we consider that the obtained results are adequate for the previously defined purposes. The results suggest that this procedure could be successfully applied for the simultaneous determination of ASA and CAF without the interference of each other and the matrix effect. The method is inexpensive and requires simple laboratory equipment.

CONCLUSION

The proposed UV-derivative method was an analytical procedure successfully used to the simultaneously quantification of ASA and CAF in commercial tablets. This kind of methods avoid the use of toxic dissolvents such as those used by chromatographic methods or expensive laboratory equipment requiring specialized maintenance. The proposed method is an analytical procedure that can be easily adopted for routine analysis of ASA and CAF mixture. The method is rapid, simple, and inexpensive without the need of high-cost investment.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Kouskova L, Leitner J. DSC study of the system o-acetylsalicylic acid–caffeine and thermodynamic modelling of the system o-acetylsalicylic acid–caffeine–paracetamol. Thermochimica Acta. 2019 Apr;674:63-7. doi: 10.1016/j.tca.2019.02.007.
2. Al-Malah KI. Optimization of drug solubility using aspen plus: acetylsalicylic acid (aspirin) solubility–A second case study. Asian J Pharm Clin Res. 2020 Apr 7;13(4):178-84. doi: 10.22159/ajpcr.2020.v13i4.37143.
3. Ghadimi H, MA Tehrani R, Basirun WJ, Ab Aziz NJ, Mohamed N, Ab Ghani S. Electrochemical determination of aspirin and caffeine at MWCNTs-poly-4-vinylpyridine composite modified electrode. J Taiwan Inst Chem Eng. 2016 Aug;65:101-9. doi: 10.1016/j.jtice.2016.05.043.
4. Tavares C, Sakata RK. Caffeine in the treatment of pain. Rev Bras Anestesiol. 2012 May-Jun;62(3):387-401. doi: 10.1016/S0034-7094(12)70139-3, PMID 22656684.
5. Grama P, Oltea MP, Zah CA. Effect of caffeine in pain management. Acta Marisiensis Ser Med. 2020;66(3):127-31.
6. Dressman JB, Nair A, Abrahamsson B, Barends DM, Groot DW, Kopp S. Biowaiver monograph for immediate-release solid oral dosage forms: acetylsalicylic acid. J Pharm Sci. 2012 Aug;101(8):2653-67. doi: 10.1002/jps.23212, PMID 22674043.
7. Williams HD, Barrett DA, Ward R, Hardy IJ, Melia CD. A liquid chromatography method for quantifying caffeine dissolution from pharmaceutical formulations into colloidal, fat-rich media. J Chromatogr B Anal Technol Biomed Life Sci. 2010 Jul 1;878(21):1739-45. doi: 10.1016/j.jchromb.2010.04.032, PMID 20483672.
8. Food and Drug Administration. Guidance for Industry: waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a Biopharmaceutics Classification System; 2017. Available from: https://collections.nlm.nih.gov/catalog/nlm:nlmuid-101720038-pdf. [Last accessed on 15 Apr 2022]
9. United States Pharmacopeia and national formulary USP43-NF38; The United States pharmacopeial convention. Rockville, MD: Inc; 2020.
10. Yadav S, Rao J. RP-HPLC method for simultaneous estimation of aspirin, ramipril, hydrochlorothiazide, simvastatin and atenolol from pharmaceutical dosage form. Int J Pharm Pharm Sci. 2014 Sep 1;6(9):443-8.
11. Pisal P, Nigade G, Kale A, Pawar S. Development and validation of stability indicating RP-HPLC method for simultaneous determination of aspirin, rosuvastatin, clopidogrel in bulk and pharmaceutical dosage form. Int J Pharm Pharm Sci. 2018 Oct 1;10(10):51-6. doi: 10.22159/ijpps.2018v10i10.28329.
12. Martin MJ, Pablos F, Gonzalez AG. Simultaneous determination of caffeine and non-steroidal anti-inflammatory drugs in pharmaceutical formulations and blood plasma by reversed-phase HPLC from linear gradient elution. Talanta. 1999 Jun 14;49(2):453-9. doi: 10.1016/S0039-9140(99)00006-5, PMID 18967618.
13. Moreira AB, Dias ILT, Neto GO, Zagatto EAG, Ferreira MMC, Kubota LT. Solid-phase spectrofluorimetric determination of acetylsalicylic acid and caffeine in pharmaceutical preparations using partial least-squares multivariate calibration. Talanta. 2005 Jul 15;67(1):65-9. doi: 10.1016/j.talanta.2005.02.004, PMID 18970138.
14. Faria EO, Lopes Junior ACV, Souto DEP, Leite FRF, Damos FS, de Cassia Silva Luz R. Simultaneous determination of caffeine and acetylsalicylic acid in pharmaceutical formulations using a boron-doped diamond film electrode by differential pulse voltammetry. Electroanalysis. 2012 May;24(5):1141-6. doi: 10.1002/elan.201200018.
15. Goyal RN, Bishnoi S, Agrawal B. Electrochemical sensor for the simultaneous determination of caffeine and aspirin in human urine samples. J Electroanal Chem. 2011 Jun;655(2):97-102. doi: 10.1016/j.jelechem.2011.03.008.
16. Sanchez Rojas F, Bosch Ojeda C. Recent development in derivative ultraviolet/visible absorption spectrophotometry: 2004-2008: a review. Anal Chim Acta. 2009 Mar 2;635(1):22-44. doi: 10.1016/j.aca.2008.12.039, PMID 19200476.
17. Bosch Ojeda C, Sanchez Rojas F. Recent applications in derivative ultraviolet/visible absorption spectrophotometry: 2009-2011. Microchem J. 2013 Jan;106:1-16. doi: 10.1016/j.microc.2012.05.012.
18. Lotfy HM, Saleh SS. Recent development in ultraviolet spectrophotometry through the last decade (2006-2016): a review. Int J Pharm Pharm Sci. 2016 Aug;8(10):40-56. doi: 10.22159/ijpps.2016v8i10.13537.
19. Listado Actualizado de Medicamentos de Referencia 2020/01. Cofepris. Mexico. Available from: https://www.gob.mx/cms/uploads/attachment/file/657152/lMR_2021_01_actualizacion_13_de_julio_de__2021.pdf. [Last accessed on 15 Apr 2022]
20. ICH. Harmonised tripartite guideline. Q2B validation of analytical procedures: methodology; 1996. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q2b-validation-analytical-procedures-methodology. [Last accessed on 15 Apr 2022]
21. Podczeck F. Comparison of *in vitro* dissolution profiles by calculating mean dissolution time (MDT) or mean residence time (MRT). Int J Pharm. 1993 Aug 15;97(1-3):93-100. doi: 10.1016/0378-5173(93)90129-4.
22. Anderson NH, Bauer M, Boussac N, Khan Malek R, Munden P, Sardaro M. An evaluation of fit factors and dissolution efficiency for the comparison of *in vitro* dissolution profiles. J Pharm Biomed Anal. 1998 Aug;17(4-5):811-22. doi: 10.1016/s0731-7085(98)00011-9, PMID 9682166.
23. Cardot JM, Beyssac E, Alric M. *In vitro-in vivo* correlation: importance of dissolution in IVIVC. Diss Technol. 2007 Feb;14(1):15-9. doi: 10.14227/DT140107P15.
24. Zhang Y, Huo M, Zhou J, Zou A, Li W, Yao C. DD Solver: an add-in program for modeling and comparison of drug dissolution profiles. AAPS J. 2010 Sep;12(3):263-71. doi: 10.1208/s12248-010-9185-1, PMID 20373062.
25. Liu X, Liu S, Wu J, Fang Z. Simultaneous monitoring of aspirin, phenacetin and caffeine in compound aspirin tablets using a sequential injection drug-dissolution testing system with partial least squares calibration. Anal Chim Acta. 1999 Jun;392(2-3):273-81. doi: 10.1016/S0003-2670(99)00235-4.