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High Performance Liquid Chromatographic Determination of the Ternary Mixture of Caffeine, Dipyrone and Drotaverine Hydrochloride in Tablets Dosage Form

Tarek S. Belal [1*], Essam F. Khamis [1], Fawzy A. El Yazbi [1] and Mohamed M.A. Hamdy [2]

[1]Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, University of Alexandria, Elmessalah 21521, Alexandria, Egypt.
[2]Analytical and Pharmaceutical Chemistry Department, Faculty of Pharmacy and Drug Manufacturing, Pharos University in Alexandria, Canal El-Mahmoudia Street, Smouha, Alexandria, Egypt.

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ABSTRACT

This work describes a simple, rapid, and reliable HPLC method for the simultaneous determination of caffeine (CAF), dipyrone (DIP) and drotaverine hydrochloride (DRV). Chromatographic separation was achieved using a reversed phase Waters Symmetry C18 (3.9×150 mm, 5 µm particle size) column with gradient elution of the mobile phase composed of 0.05 M orthophosphoric acid and acetonitrile. The gradient elution started with 15% (by volume) acetonitrile ramped up linearly to 60% in 3 min then kept at this percentage till the end of the run. The flow rate was 1mL/min. Quantification was based on measuring peak areas at 210 nm. The analytes were resolved with retention times 1.47, 2.39 and 7.17 min for DIP, CAF and DRV, respectively. Analytical performance of the proposed procedure was validated with respect to system suitability, linearity, ranges, precision, accuracy, robustness, detection and quantification limits. The linearity ranges were 10-200, 5-100 and 5-100 µg/mL for DIP, CAF and DRV, respectively. The validated HPLC method was applied to the simultaneous determination of the three drugs in several laboratory-prepared mixtures of different ratios. Finally, laboratory made tablets containing the three drugs were assayed using the developed procedure where no interfering peaks were encountered from the tablet additives.

INTRODUCTION

Caffeine (CAF) (Figure 1), chemically known as 1,3,7-trimethylpurine-2,6(3*H*,1*H*)-dione, is a CNS stimulant, particularly the higher centres, and it can produce a condition of wakefulness and increased mental activity. It may also stimulate the respiratory centre, increasing the rate and depth of respiration. Caffeine facilitates the performance of muscular work and increases the total work that can be performed by a muscle. Caffeine has been widely used in analgesic preparations to enhance the effects of both non-opioid and opioid analgesics (Sweetman, 2009). Determination of CAF in various matrices was addressed in many reports. Analytical methodology in these reports involved the use of voltammetry (Gao *et al.*, 2013; Gupta *et al.*, 2013), ^{1}H NMR spectrometry (delCampo *et al.*, 2010), near infrared spectroscopy (Zhang *et al.*, 2013), spectrophoyometry (Kelani, 2005; Khoshayand *et al.*, 2008), (Moreira *et al.*, 2006), TLC (Bocheńska *et al.*, 2013), two dimensional gas chromatography-mass spectrometry (Lima Gomes *et al.*, 2013) and capillary electrophoresis (Kartsova *et al.*, 2010).

In addition, liquid chromatography was widely applied. Examples of these reports are HPLC with UV detection (Kartal, 2001; Perera *et al.*, 2010), HPLC with photodiode array detection (Alvi and Hammami, 2011) and UPLC-MS-MS (Liu *et al.*, 2013). Dipyrone (also known as metamizole sodium) (DIP) (Figure 1), chemically known as sodium *N*-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-*N* methyl amino methanesulphonate monohydrate, is a non-steroidal anti-inflammatory drug.

It has an analgesic effect, and mainly used in severe pain or fever (Sweetman, 2009). DIP was assayed by a variety of analytical techniques including the use of voltammetry (Baranowska *et al.*, 2008), diffuse reflectance spectroscopy (Weinert *et al.*, 2007), near infrared spectroscopy (Sanches *et al.*, 2012), chemiluminescence (Pradana Pérez *et al.*, 2012) and

* *Corresponding Author*
Tarek S. Belal, Phone: +203 4871317 ,
Fax: +203 4873273, E-mail : tbelaleg@yahoo.com

spectrophotometry (Do Nascimento *et al.*, 2007; Morelli, 2003; Suarez *et al.*, 2011). In addition, separation techniques were applied such as HPTLC (Aburjai *et al.*, 2000), HPLC-MS-MS (Penney *et al.*, 2005) and HPLC-diode array detection (Salmerón-Gacía *et al.*, 2009; Senyuva *et al.*, 2005).

Drotaverine hydrochloride (DRV) (Figure 1), chemically known as 1-(3,4-diethoxybenzylidene)-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, is used as an antispasmodic in the management of biliary-tract, urinary-tract and gastrointestinal spasm (Sweetman, 2009). Several methods were described in the literature for the determination of DRV in pharmaceutical formulations and/or biological fluids. These methods include potentiometric flow injection analysis (Ibrahim *et al.*, 2005), voltammetry (Zayed and Issa, 2009), spectrophotometry (Abdellatef *et al.*, 2007; Ragupathy and Arcot, 2013), spectrofluorimetry (El-Wasseef *et al.*, 2008), TLC (Abdellatef *et al.*, 2007), HPLC with UV detection (Dahivelkar *et al.*, 2012) and HPLC-diode array detection (Maher and Belal, 2012).

The analysis of ternary mixtures containing CAF and DRV together with paracetamol was described in few analytical reports. These reports proposed spectrophotometric (El-Gindy *et al.*, 2010; Metwally *et al.*, 2007), TLC (Metwally *et al.*, 2007) and HPLC-UV (El-Gindy *et al.*, 2010; Issa *et al.*, 2012) procedures. Similarly, mixtures containing CAF and DIP were analyzed using spectrophotometric (Dinç and Onur, 1998), HPTLC (Aranda and Morlock, 2007) and HPLC-UV (Altun, 2002) methods.

The triple combination of CAF, DIP and DRV is a very effective and powerful pain killer; marketed under the trade name Quarelin® in some countries (Sweetman, 2009). To the best of our knowledge, no attempts have been made to assay this combination of drugs by any analytical methodology. This study describes a simple, rapid and reliable HPLC-UV method for the simultaneous determination of CAF, DIP and DRV in bulk form and in tablets dosage form.

MATERIALS AND METHODS

Instrumentation

The HPLC system comprised of Perkin-Elmer Series 200 (pump, UV/Visible detector, auto sampler and vacuum degasser) with a Perkin-Elmer chromatography interface Series 600 connected to a computer loaded with TotalChrom Workstation Perkin-Elmer Chromatography software. Chromatographic separation was accomplished using Reversed phase Waters Symmetry C18 (3.9×150 mm, 5 µm particle size) column.

Materials

Authentic samples of caffeine (CAF), dipyrone (DIP) and drotaverine hydrochloride (DRV) were kindly provided by Alexandria Pharmaceuticals Co., Alexandria, Egypt. HPLC grade acetonitrile and methanol (LAB-SCAN analytical sciences, Poland), analytical grade orthophosphoric acid and high purity distilled water were used. The formulation assayed in the study was laboratory-made tablets each containing 60 mg CAF, 400 mg DIP and 40 mg DRV. Inactive ingredients used in the preparation of tablets (maize starch, microcrystalline cellulose "Avicel", magnesium stearate, hydroxypropylmethylcellulose "HPMC" and colloidal silica "Aerosil") were obtained from Pharco Pharmaceuticals Co., Alexandria, Egypt.

General procedure

A mobile phase consisting of (A) 0.05 M orthophosphoric acid and (B) acetonitrile was used. The separation was achieved with a linear gradient program as follows: 15 % v/v B at zero time; from 0 to 3 min, ramp up to 60 % v/v B; from 3 to 10 min, holding 60 % v/v B. After 10 min, the gradient program was returned to the initial conditions and the analytical column was reconditioned for 3 min. The mobile phase was filtered using a 0.45 µm pore size membrane filter prior to use. The flow rate was 1.0 mL/min. The injection volume was 20 µL. The UV detector was set at 210 nm. All determinations were performed at 25ºC. CAF, DIP and DRV stock solutions (1000 µg/mL) were prepared in HPLC grade methanol. The working solutions were prepared by dilution of the stock solutions with distilled water to reach the concentration ranges 5–100, 10–200 and 5–100 µg/mL for CAF, DIP and DRV, respectively. Triplicate 20 µL injections were made for each concentration and were chromatographed using the previously described chromatographic conditions. The peak areas at 210 nm were plotted against the corresponding concentrations to construct the calibration graphs.

Assay of laboratory made tablets

Ten laboratory made tablets were accurately weighed and finely powdered. A weighed amount of the powdered tablets equivalent to 15 mg CAF, 100 mg DIP and 10 mg DRV was extracted into 60 mL methanol, sonicated for 30 minutes then filtered into a 100-mL volumetric flask. The residue was washed with two 10-mL portions of methanol and washings were added to the filtrate. Then dilution to volume was made with methanol to reach a final concentration of 150 µg/mL CAF, 1000 µg/mL DIP and 100 µg/mL DRV. Aliquots of the tablet extract were diluted with distilled water to obtain final concentrations within the specified ranges then were treated as under general procedure. The recovered concentrations were calculated using corresponding external standards. For standard addition assay, sample solutions were spiked with aliquots of the stock standard solutions to obtain total concentrations within the previously specified ranges then were treated as under general procedure. The recovered concentrations were calculated by comparing the analyte response with the increment response attained after addition of the standard.

RESULTS AND DISCUSSION

Optimization of chromatographic conditions

A gradient HPLC-UV detection method was developed to provide simple, rapid and reliable quality control analysis of CAF, DIP and DRV mixture in pharmaceutical preparations. The most important aspect in liquid chromatography method

development is the achievement of sufficient resolution with acceptable peak symmetry in a reasonable analysis time. For optimization of the stationary phase, several reversed phase columns namely Waters Symmetry C18 (3.9×150 mm, 5 µm particle size), Hypersil Shandon C18 (4.6×250 mm, 5 µm), Thames Restek UK limited C18 (3.9×150 mm, 5 µm), Brownlee Spheri-5 C18 (4.6×220 mm, 5 µm) (PerkinElmer) and Brownlee Spheri-5 C8 (4.6×220 mm, 5 µm) (PerkinElmer) were tested. The use of these columns allowed the resolution of the analytes. However, the Waters Symmetry C18 showed better peak shapes within a reasonable run time, hence, it became the column of choice for this study. Several mobile phases were evaluated using various proportions of different aqueous phases and organic modifiers. The best mobile phase combination was 0.05M orthophosphoric acid solution and acetonitrile. Methanol was tried as an organic modifier and orthophosphoric acid solution was substituted by other aqueous phases such as water or acetic acid solution. In these trials, DRV suffered from increased retention times and some chromatograms showed poor peak shape and excessive tailing for some drugs. Isocratic elution of different proportions of 0.05M phosphoric acid and acetonitrile did not provide satisfactory separation due to either inadequate resolution between the successive CAF and DIP peaks or delayed DRV peak. To overcome these complications, gradient elution was applied. Several gradient programs were tried and the best compromise between adequate resolution and reasonable retention times was achieved using a gradient system starting with 15% (by volume) acetonitrile ramped up linearly to 60% in 3 min then kept at this percentage afterward. Flow rate was kept constant at 1 mL/min all over the run. The three dugs exhibit different absorption characteristics, however 210 nm was found suitable for measurement of the 3 drugs, and thus it was selected for quantification. The three drugs showed almost symmetric peaks at 210 nm with acceptable retention times: 1.47, 2.39 and 7.17 min for DIP, CAF and DRV respectively (Figure 2). Resolution (Rs) is a measure of the degree of separation between adjacent peaks and a value of 1.5 implies a complete separation between two consecutive peaks. Resolution value was 3.56 between DIP and CAF peaks, and 17.20 between CAF and DRV peaks.

Validation of the proposed method

The proposed method was validated according to the International Conference on Harmonization (ICH) guidelines on validation of analytical procedures (ICH, 2005).

Linearity and concentration ranges

Linearity of the proposed HPLC procedure was evaluated by analyzing a series of different concentrations for each compound. The linear regression equations were generated by least squares treatment of the calibration data. Under the aforementioned optimized conditions, the measured peak areas were found to be proportional to the drugs' concentrations. Table 1 presents the performance data and statistical parameters including intercepts and slopes of the regression equations, concentration ranges, correlation coefficients, standard deviations of the intercept (S_a), slope (S_b), and residuals ($S_{y/x}$). Calibration curves showed good linear relationships over the concentration ranges of 5-100, 10-200 and 5-100 µg/mL for CAF, DIP and DRV, respectively, as judged by the correlation coefficient values which were not less than 0.9994 and the RSD% of the slope values which did not exceed 2%.

Limits of detection and quantification

Limit of detection (LOD) is defined as the concentration of the analyte which has a signal-to-noise ratio of 3:1. For the limit of quantification (LOQ), the ratio considered is 10:1. The LOD and LOQ values of CAF, DIP and DRV were calculated using the signal-to-noise ratio method and are shown in Table 1. Both LOD and LOQ values confirm the sensitivity of the proposed HPLC method.

Accuracy and precision

The within-day (intra-day) precision and accuracy for the proposed method were studied at three concentration levels (60, 80 and 100 µg/mL) for CAF, DIP and DRV using three replicate determinations for each concentration within one day. Similarly, the between-day (inter-day) precision and accuracy were tested by analyzing the same three concentrations using three replicate determinations repeated on three days. The recovered concentrations were calculated using the corresponding regression equations and were found to be satisfactory. The percentage relative standard deviation (RSD %) values were less than 1.8% and percentage relative error (Er %) values were less than 2.4% proving the high precision and accuracy of the developed method for the estimation of each drug in bulk form (Table 2).

Selectivity

Method selectivity was examined by preparing several laboratory-prepared mixtures of the three compounds at various concentrations within the specified linearity ranges. The laboratory-prepared mixtures were analyzed according to the previously described procedure. The recovered concentrations, percentage relative standard deviation (RSD %) and percentage relative error (Er %) values shown in Table 3 were satisfactory thus validating the selectivity, precision and accuracy of the developed method and demonstrating its capability to resolve and quantify the three drugs in mixtures of different ratios.

Robustness

Robustness was examined by evaluating the influence of small variations in different conditions such as concentration of orthophosphoric acid solution (± 0.005 M), ratio of acetonitrile in the gradient program (± 2 %), source of acetonitrile (LAB-SCAN analytical sciences, Poland or SDS, France), detector wavelength (± 2 nm), and flow rate (± 0.05 mL/min). These variations did not have any significant effect on the measured responses or the chromatographic resolution. RSD(%) of the measured peak areas using these variations did not exceed 2%.

Table. 1: Analytical parameters for the determination of CAF-DIP-DRV mixture using the proposed HPLC method.

Parameter	CAF	DIP	DRV
Concentration range (µg/mL)	5 – 100	10 – 200	5 – 100
Intercept (a)	612.0	232.3	401.0
Slope (b)	137.89	35.79	72.38
Correlation coefficient (r)	0.9996	0.9994	0.9996
S_a (1)	145.93	47.00	74.56
S_b (2)	2.20	0.71	1.12
RSD% of the slope (S_b%)	1.60	1.98	1.55
$S_{y/x}$ (3)	139.14	44.81	71.09
LOD (4) (µg/mL)	0.41	1.70	0.48
LOQ (5) (µg/mL)	1.36	5.68	1.61

(1) S_a: Standard deviation of intercept
(2) S_b: Standard deviation of slope
(3) $S_{y/x}$: Standard deviation of residuals
(4) Limit of detection
(5) Limit of quantification

Table. 2: Precision and accuracy for the determination of CAF, DIP and DRV in bulk form using the proposed HPLC method.

Drug	Parameter	Nominal value (µg/mL)	Found ± SD[a] (µg/mL)	RSD(%)[b]	E_r(%)[c]
CAF	Within-day	60	60.08 ± 0.18	0.30	0.13
		80	81.06 ± 0.22	0.27	1.33
		100	99.09 ± 0.15	0.15	-0.91
	Between-day	60	59.66 ± 0.79	1.32	-0.57
		80	79.39 ± 1.40	1.76	-0.76
		100	99.35 ± 0.27	0.27	-0.65
DIP	Within-day	60	60.58 ± 0.38	0.63	0.97
		80	80.85 ± 0.17	0.21	1.06
		100	99.61 ± 1.10	1.10	-0.39
	Between-day	60	60.59 ± 0.74	1.22	0.98
		80	80.85 ± 0.56	0.69	1.06
		100	99.82 ± 0.92	0.92	-0.18
DRV	Within-day	60	60.72 ± 0.20	0.33	1.20
		80	81.58 ± 0.89	1.09	1.98
		100	100.75 ± 1.68	1.67	0.75
	Between-day	60	60.82 ± 0.61	1.00	1.37
		80	81.88 ± 0.93	1.14	2.35
		100	100.59 ± 1.51	1.50	0.59

[a] Mean ± standard deviation for three determinations.
[b] % Relative standard deviation.
[c] % Relative error.

Table 3: Determination of CAF-DIP-DRV laboratory-prepared mixtures using the proposed HPLC method.

Nominal value (µg/mL)			Found ± SD[a] (µg/mL)			RSD(%)[b]			E_r(%)[c]		
CAF	DIP	DRV	CAF	DIP	DRV	CAF	DIP	DRV	CAF	DIP	DRV
5	10	5	5.10 ± 0.07	10.07 ± 0.12	5.08 ± 0.05	1.37	1.19	0.98	2.00	0.70	1.60
15	50	10	15.09 ± 0.14	49.28 ± 0.79	10.17 ± 0.21	0.93	1.60	2.06	0.60	-1.44	1.70
10	200	10	9.89 ± 0.14	199.24 ± 0.41	10.03 ± 0.06	1.42	0.21	0.60	-1.10	-0.38	0.30
15	100	10	15.19 ± 0.29	99.84 ± 0.61	10.13 ± 0.16	1.91	0.61	1.58	1.27	-0.16	1.30
30	100	20	29.64 ± 0.41	101.26 ± 0.93	20.29 ± 0.33	1.38	0.92	1.63	-1.20	1.26	1.45
100	100	100	100.94 ± 0.71	99.76 ± 0.12	101.14 ± 0.48	0.70	0.12	0.48	0.94	-0.24	1.14

[a] Mean ± standard deviation for three determinations.
[b] % Relative standard deviation.
[c] % Relative error.

Table. 4: Application of the proposed HPLC method to the analysis of CAF-DIP-DRV mixture in laboratory made tablets.

Parameter	External standard method		
	CAF	DIP	DRV
%Recovery ± SD[a]	100.75 ± 0.86	101.31 ± 1.84	101.04 ± 1.13
RSD(%)[b]	0.85	1.82	1.12
E_r(%)[c]	0.75	1.31	1.04
Parameter	**Standard addition method**		
	CAF	DIP	DRV
%Recovery ± SD[a]	100.67 ± 0.37	100.29 ± 0.56	101.13 ± 0.48
RSD(%)[b]	0.37	0.56	0.48
E_r(%)[c]	0.67	0.29	1.13

[a] Mean ± standard deviation for five determinations.
[b] % Relative standard deviation.
[c] % Relative error.

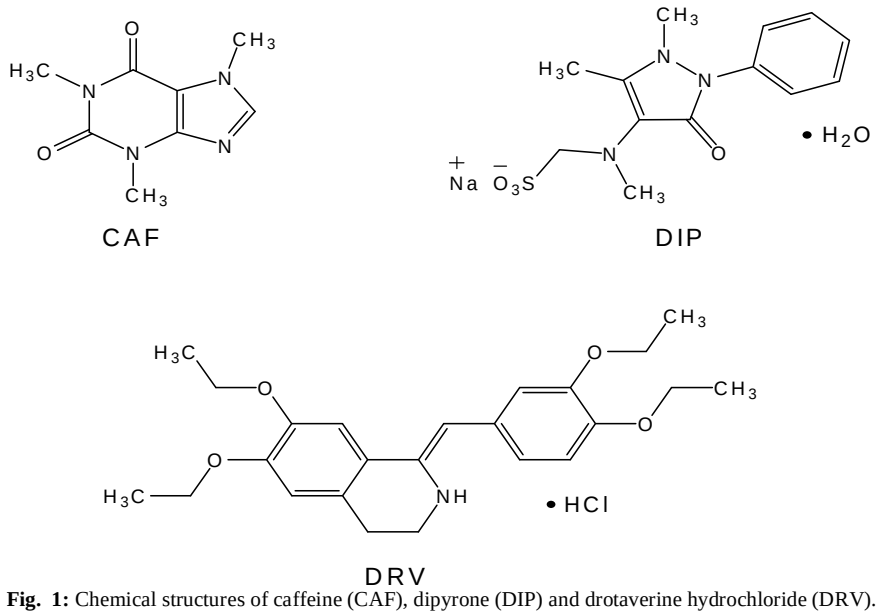

Fig. 1: Chemical structures of caffeine (CAF), dipyrone (DIP) and drotaverine hydrochloride (DRV).

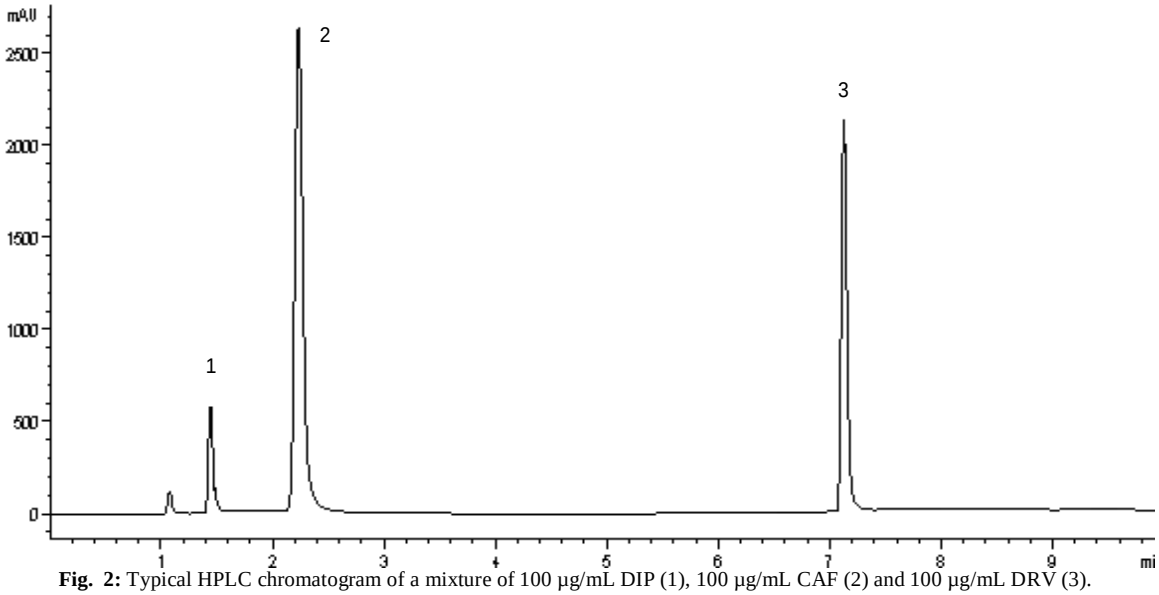

Fig. 2: Typical HPLC chromatogram of a mixture of 100 µg/mL DIP (1), 100 µg/mL CAF (2) and 100 µg/mL DRV (3).

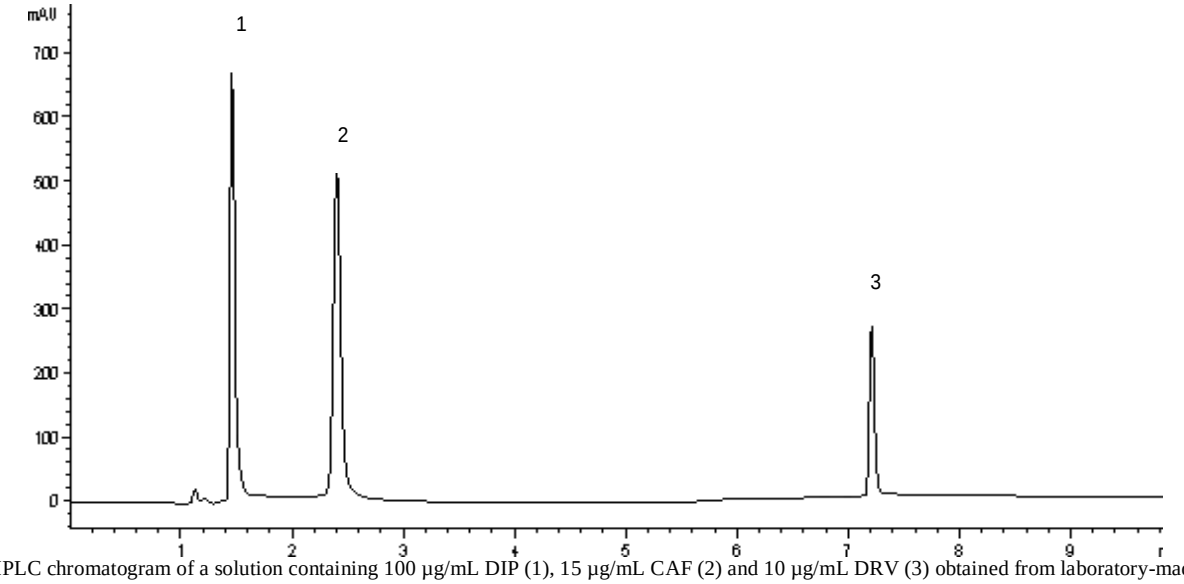

Fig. 3: HPLC chromatogram of a solution containing 100 µg/mL DIP (1), 15 µg/mL CAF (2) and 10 µg/mL DRV (3) obtained from laboratory-made tablets.

Stability of solutions

The stability of standard working solutions as well as sample solutions of the three drugs in distilled water was examined, and no chromatographic changes were observed within 5 hours at room temperature. Also, the stock solutions prepared in methanol were stable for at least one week when stored refrigerated at 4ºC. Retention times and peak areas of the drugs remained unchanged during these periods.

Analysis of tablets

The developed HPLC method was applied for the assay of the ternary mixture in the laboratory-made tablets. The active ingredients were extracted with the same solvent used for the preparation of the standard stock solutions (methanol) then dilution was made with distilled water to reach concentration levels within the specified ranges. A representative chromatogram obtained from the tablets solution is shown in Figure 3 where the three active ingredients eluted at their specific retention times. No interfering peaks were observed from any of the inactive ingredients. Recoveries were calculated using both external standard and standard addition methods. The assay results revealed satisfactory accuracy and precision as indicated from % recovery, SD and RSD% values (Table 4). It is evident from these results that the proposed method is applicable to the assay of this fixed dose combination with minimum sample preparation and satisfactory levels of accuracy and precision.

CONCLUSIONS

In this study, a simple, rapid and reliable HPLC method was described for the assay of the ternary mixture of caffeine, dipyrone and drotaverine hydrochloride. To the best of our knowledge, there are no analytical reports describing the simultaneous determination of the three drugs in their combined dosage form. The analytes were successfully resolved and quantified using a RP-C18 column in a relatively short run time (less than 8 min). Consequently, the described method can be considered cost- and time-effective. Reliability was guaranteed by testing various validation parameters of the method and by successful application to laboratory-made tablets. Hence, it can be recommended for the routine quality control of the studied drugs either in bulk form or in their combined tablets dosage form.

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