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Article

A Simplified Reflectometric Method for the Rapid Determination of Dipyrone in Pharmaceutical Formulations

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Este artigo descreve um método simples, portátil e ambientalmente amigável para a rápida determinação de dipirona em medicamentos empregando a espectroscopia de reflectância difusa. O método proposto está baseado nas medidas de reflectância do composto alaranjado produzido na reação de *spot-test* entre dipirona e *p*-dimetilaminocinamaldeído (*p*-DAC), em meio ácido, usando papel de filtro como suporte sólido. Metodologias de planejamento de experimentos foram utilizadas para a otimização das condições experimentais. Todas as medidas de reflectância foram efetuadas em 510 nm e o intervalo linear foi de $1{,}42 \times 10^{-4}$-$2{,}85 \times 10^{-3}$ mol L^{-1}, com coeficiente de correlação de 0,999. Os limites de detecção (LOD) e de quantificação (LOQ) foram de $1{,}20 \times 10^{-5}$ mol L^{-1} e $4{,}00 \times 10^{-5}$ mol L^{-1}, respectivamente. A precisão intradia e interdia foi avaliada na análise de uma solução de dipirona $7{,}90 \times 10^{-4}$ mol L^{-1} (n = 10). Os coeficientes de variação foram 1,1 e 0,9%, respectivamente. O método proposto foi aplicado com êxito na determinação de dipirona em amostras comerciais de medicamentos. Não foram observadas interferências dos excipientes comuns em formulações farmacêuticas. Os resultados obtidos pelo método proposto estão em boa concordância com aqueles obtidos pelo procedimento da Farmacopéia Brasileira num nível de confiança de 95%.

This paper describes a simple, portable and environmentally friendly method for the rapid determination of dipyrone in pharmaceuticals by using diffuse reflectance spectroscopy. The proposed method is based on the reflectance measurements of the orange compound produced from the spot test reaction between dipyrone and *p*-dimethylaminocinnamaldehyde (*p*-DAC), in acid medium, using a filter paper as solid support. Experimental design methodologies were used to optimize the measurement conditions. All reflectance measurements were carried out at 510 nm and the linear range was from 1.42×10^{-4}-2.85×10^{-3} mol L^{-1}, with a correlation coefficient of 0.999. The limit of detection (LOD) and the limit of quantification (LOQ) were 1.20×10^{-5} mol L^{-1} and 4.00×10^{-5} mol L^{-1}, respectively. The intraday precision and interday precision were studied for 10 replicate analyses of 7.90×10^{-4} mol L^{-1} dipyrone solution. The coefficients of variation were 1.1 and 0.9%, respectively. The proposed method was applied successfully to the determination of dipyrone in commercial brands of pharmaceuticals. No interferences were observed from the common excipients in formulations. The results obtained by the proposed method were favorably compared with those given by the Brazilian Pharmacopoeia procedure at 95% confidence level.

Keywords: dipyrone, reflectance spectroscopy, spot test, pharmaceutical formulations

Introduction

A great problem in the whole world is the falsification and adulteration of medicines consumed by the population.[1] The use of these medicines represents a risk for people's health. In Brazil, this problem was also detected in 1998, when a variety of medicines such as contraceptives, antibiotics as well as antipyretics with dipyrone in its composition were falsified.[1,2] So, the analysis of pharmaceutical formulations has an objective not only for the industrial quality control, but also for the product idoneousness proof.[3]

Dipyrone (sodium salt of 1-phenyl-2,3-dimethyl-4-methylaminomethane sulphonate-5-pyrazolone; analgin, novalgin, metamizol) is a therapeutic agent commonly used as analgesic, antipyretic and antispasmodic in

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several pharmaceutical formulations.[4] It was introduced into clinical practice in 1922 and is still in use in many countries,[5] due to its strong analgesic effect, available parenteral formulation and low cost. Dipyrone is widely used in Europe and South America, and it constitutes a standard analgesic drug in Brazil.[6]

Several analytical methods have been reported for the quantitative determination of dipyrone in pharmaceutical formulations, including titrimetry in aqueous[7,8] and non-aqueous[9] media, high-pressure liquid chromatography with UV detection,[10-12] voltammetry,[13] polarography,[14] chemilumimetry[15] and spectrophotometry.[2,16-20]

In recent years more and more strict regulations related to the quality control of pharmaceuticals led to increasing demands on the simplicity and rapidity of analytical assays. [15,21] Considering the simplicity of the spot test method, the use of small quantities of chemicals, the confidence and the rapidity of such kind of procedure, the quantitative spot test analysis by diffuse reflectance spectroscopy could be interesting to develop analytical procedures for analysis of drugs in pharmaceuticals formulations.

Some methods reported in the literature showed that the appropriate use of diffuse reflectance spectroscopy could yield reliable results evidencing the potential of this technique for quantitative analysis.[3,22-29] To the best of our knowledge, there are no reports on the use of the reflectance analytical methods for the determination of dipyrone in pharmaceuticals.

The combined spot test-diffuse reflectance spectroscopy offers advantages over other methods, such as simplicity and extremely low consumption of reagents. Moreover, the reflectance measurements can be performed in locus by using a very simple homemade reflectometer or a portable diffuse reflectance spectrophotometer, which are small, lightweight, inexpensive and battery operated, characteristics highly attractive for many applications in any location by nearly everyone.[30]

The aim of the present work has been to develop a simple, portable and environmentally friendly[31] method for the rapid determination of dipyrone in pharmaceuticals. The proposed method is based on the reflectance measurements in the visible region of the spectrum (λ_{max} = 510 nm) produced from the spot test reaction between dipyrone and *p*-dimethylaminocinnameldehyde (*p*-DAC), in acid medium, using a filter paper as solid support. Experimental design methodologies were used to optimize the measurement conditions. The results showed that it is possible to perform quantitative spot test of reasonable quality using reflectance measurements.

Experimental

Apparatus

The reflectance measurements were collected using a hand-held integrating sphere (ISP-REF, Ocean Optics, Dunedin, USA) connected to a fiber optic spectrometer (USB2000,Ocean Optics).The USB2000 spectrometer is equipped with a 2048 pixels Sony ILX511 CCD array detector. A software SpectraSuite(Ocean Optics) was used for acquisition and storage of spectra**.**

Brand (100 to 1000 μL) and Eppendorf (10 to 100 μL) micropipettes were used to measure the smaller volumes in the experiments.

Materials, reagents and solutions

High purity deionized water (resistivity 18.2 MΩ cm) obtained by using a Milli-Q plus system (Millipore Corp., Bedford, MA, USA) was used to prepare the solutions of dipyrone. Analytical-reagent or pharmaceutical grade chemicals were used. The excipients used in the interference study were of pharmaceutical grade. Whatman 1 filter paper was used as solid support. Glacial acetic acid (Mallinckrodt, Xalostoc, Mexico) was used.

Sodium dipyrone stock solution 5.70×10^{-3} mol L^{-1} was prepared daily by dissolving 100.0 mg of sodium dipyrone (Daichi Seiyaku Co. Ltd, Tokyo, Japan) in 50 mL of deionized water and standardized as described in the literature.[8] Working standard solutions (1.42×10^{-4} to 2.85×10^{-3} mol L^{-1}) were obtained by suitable dilutions of the stock solution with deionized water.

p-Dimethylaminocinnamaldehyde (*p*-DAC) (Riedel-de-haën, Germany) 0.8% (m/v) was prepared in methanol (HPLC grade, Mallinckrodt, Xalostoc, Mexico) and it was kept refrigerated for no more than 1 week.[22]

Recommended procedure

For the spot test reaction the optimized conditions obtained in the experimental designs were used. The solutions were spotted onto 2.25 cm^2 Whatman 1 filter paper. To carry out measurements, first 20 μL of the *p*-DAC 0.8% (m/v) was spotted, then 20 μL of the glacial acetic acid and finally, 10 μL of the dipyrone solution. The solutions were spotted onto the center of the filter paper using a micropipette fixed in a holder according to procedure described by Tubino *et al.*[26] The reflectance measurements were carried out at 510 nm at room temperature (25 °C). The blank was prepared in a similar way, but omitting dipyrone.

Sample preparation and analytical applications

Samples of pharmaceutical formulations containing dipyrone were purchased in local drugstores in Araraquara city (Brazil) and analyzed by the proposed method.

Solid samples: twenty tablets of each commercial brand pharmaceutical to be studied were exactly weighed and grounded to fine powder. A portion of this powder equivalent to approximately 15.0 mg of dipyrone was accurately weighed. The sample was shaken with 15 mL of deionized water in a magnetic mixer for 5 minutes and diluted with deionized water in a 50 mL volumetric flask. This solution was filtered in Whatman 42 filter paper and then an aliquot of 10 μL of this solution was taken for the spot test reflectance analysis as described in the recommended procedure.

Liquid samples: an accurately volume nominally equivalent to 250.0 mg of dipyrone, was transferred to 100 mL volumetric flask and diluted to the mark with deionized water. In the sequence, 1.00 mL of this solution was placed in a 10 mL volumetric flask and diluted to the mark with deionized water. Finally, this solution was analyzed as described in the recommended procedure.

Reference method

For accuracy assessment of the results obtained by the proposed method, dipyrone pharmaceutical formulations were analyzed by the official method of the Brazilian Pharmacopoeia.[8]

Results and Discussion

Preliminary experiments carried out in our laboratory demonstrated the formation of an orange product from reaction between dipyrone and *p*-DAC, in acid medium, on filter paper surface. The *p*-DAC is a useful analytical reagent[32] which has been utilized for the detection and spectrophotometric determination of aromatic primary and secondary amines.

Dipyrone is an aromatic tertiary amine and in aqueous solutions it readily undergoes hydrolysis,[33] forming the 4-methylaminoantipyrine a secondary aromatic amine, which can react with *p*-DAC. The reaction between secondary aromatic amines and *p*-DAC is assumed to take place through condensation of the protonated secondary amino group with the carbonyl group of the reagent to produce an imminium salt.[34,35] The probable mechanism for this reaction is shown in Scheme 1, which is to a large extent based on reactions suggested in the literature.[34,35] Figure 1 shows the reflectance spectrum of the orange product, with maximum value of A_R (optical density for reflectance measurements) at 510 nm and the reflectance spectrum of the blank.

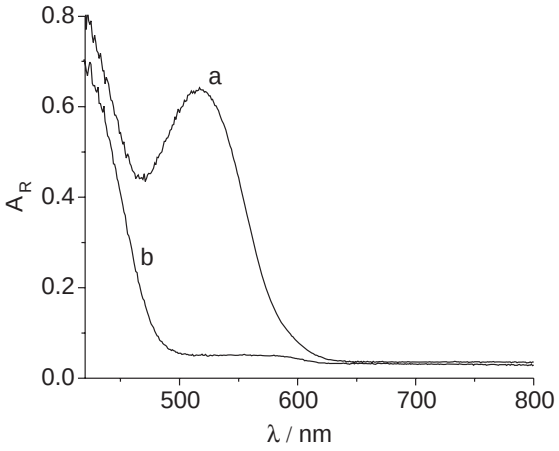


Figure 1. Reflectance spectrum a: orange product (conditions: 20 μL *p*-DAC 0.8 % (m/v); 20 μL glacial acetic acid and 10 μL dipyrone 1.42×10^{-3} mol L^{-1}) b: blank (conditions: 20 μL *p*-DAC 0.8 % (m/v); 20 μL glacial acetic acid and 10 μL H_2O). Measurements carried out at 25 °C.

Optimization of the variables

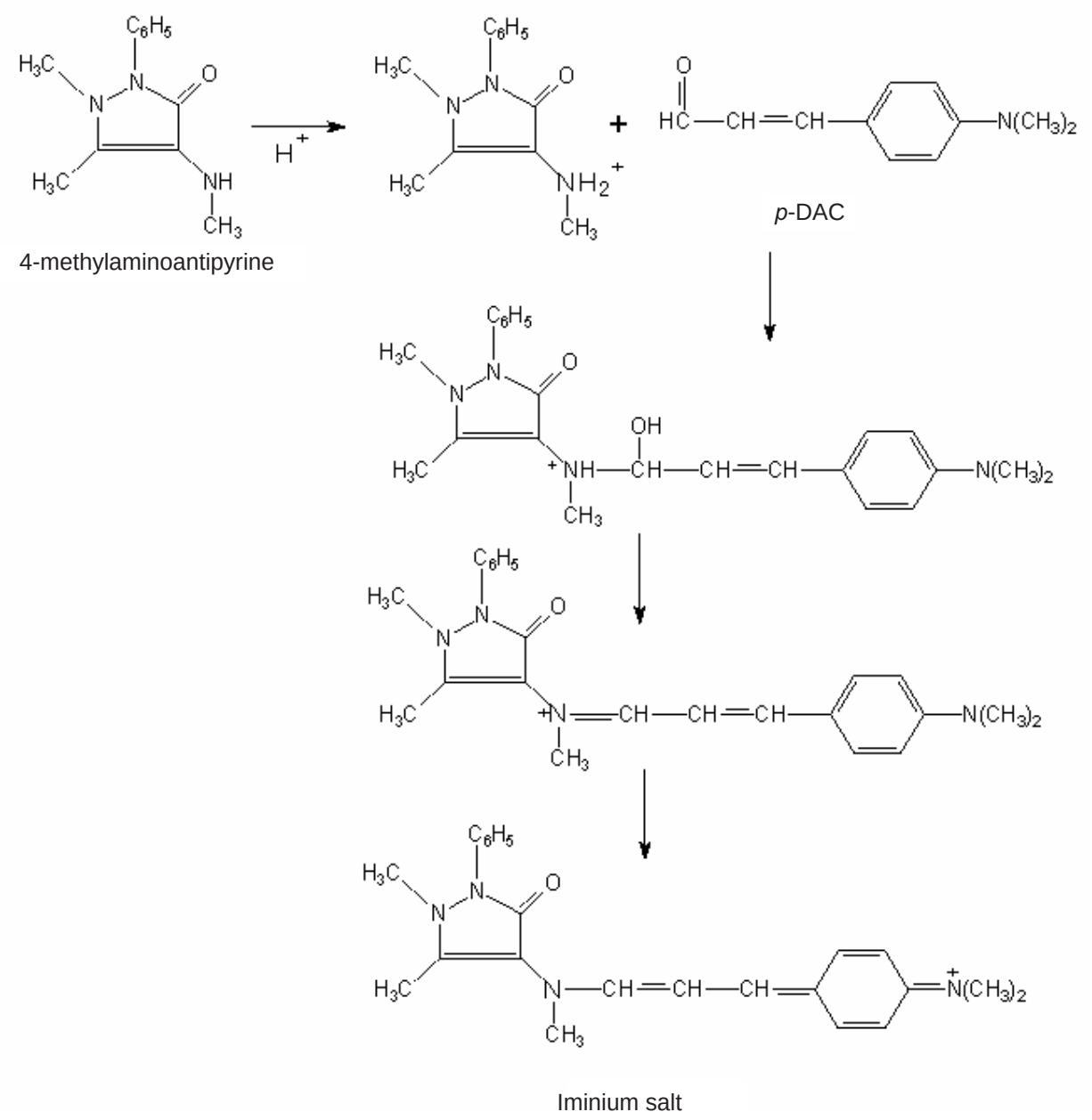
The use of the reflectance measurements for determination purposes is possible if an appropriate set of experimental conditions is selected. In order to obtain the best use from this technique, it is useful to know something about the parameters involved in the reflectance measurements. According to Wendlant and Hecht,[36] reflectance measurements are reproducible if the measured surface has constant area and the spot test color is uniform over the entire surface.

Investigations were carried out to establish the most favorable conditions for the spot test reaction on the filter paper in order to achieve maximum reflectance response at 510 nm.

Preliminary experiments were carried out in our laboratory in order to select the most favorable acid and addition order of reagents for the spot test. In these experiments were tested two acids: acetic acid and HCl, and all combinations of the addition order of the reagents also have been tested. The best results were obtained when acetic acid was used and two addition orders of reagents shown in the Table 1 were examined.

Based on these results, a full factorial design (2^3) was carried out, which allowed simultaneously studying the variables: *p*-DAC concentration, acetic acid concentration and the effect of two selected addition order of reagents.

The experimental matrix employed with the variables and its levels examined (un-coded and coded) are



Scheme 1.

Table 1. Design matrix of the full factorial design (2^3)

Run	Un-coded variables levels			Coded variables levels		
	p-DAC % (m/v) [a]	Acetic acid [a]	A.O.[c]	*p*-DAC % (m/v) [a]	Acetic acid [a]	A.O.[c]
1	0.4	1:1 [b]	X	-1	-1	-1
2	0.8	1:1 [b]	X	1	-1	-1
3	0.4	Concentrated	X	-1	1	-1
4	0.8	Concentrated	X	1	1	-1
5	0.4	1:1 [b]	Y	-1	-1	1
6	0.8	1:1 [b]	Y	1	-1	1
7	0.4	Concentrated	Y	-1	1	1
8	0.8	Concentrated	Y	1	1	1

[a] The volume spotted was fixed at 20 mL, [b] Solution obtained by dilution of glacial acetic acid with methanol (v/v), [c] Addition Order(A.O.) of the reagents: X = (*p*-DAC, Acetic acid, Dipyrone) and Y = (Dipyrone, Acetic acid, *p*-DAC)

summarized in Table 1. The runs were carried out in random order and in duplicate. In all experiments, the volume spotted of 2.85×10^{-3} mol L^{-1} dipyrone solution was kept constant in 10 μL. The designs were obtained by using Statistic program, Version 6.0.

Figure 2 represents the standardized Pareto chart which is a horizontal bar-chart. The length of each bar on the chart is proportional to the absolute value of its associated estimated effect or the standardized effect. The most significant effect corresponds to the factor addition order of the reagents, which show a best response when adjusted at negative level (-1). The results also indicated that the reflectance measurements were significantly higher where acetic acid concentration and the *p*-DAC concentration were adjusted at positive level (+1).

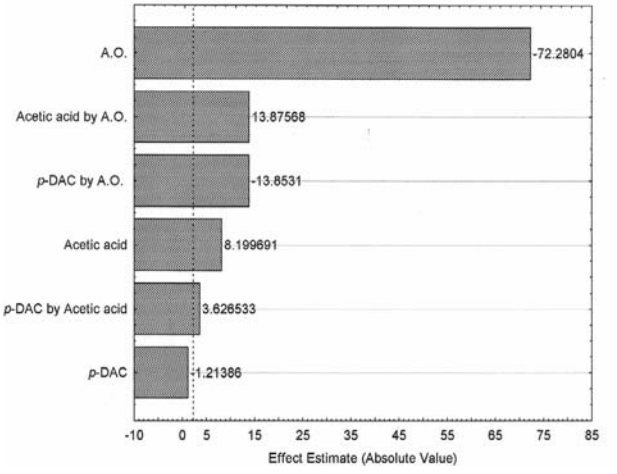


Figure 2. Standardized effects of *p*-DAC concentration, acetic acid concentration and addition order of the reagents and their interaction effects on the reflectance measurements (λ = 510 nm).

In the sequence, a central composite design was built in order to obtain the optimal conditions for determination of dipyrone by studying the effect of *p*-DAC and glacial acetic acid. In this experiment the effect of glacial acetic acid was examined by varying its added volume onto filter paper, and the effect of the *p*-DAC by varying its concentration. The variables considered and its examined levels (un-coded and coded) and the experimental matrix are given in Table 2.

A statistically significant quadratic model accounting of 87.0% of the variance was fitted to the data (95% confidence level). The resulting response surface is shown in Figure 3, as a function of glacial acetic acid volume and *p*-DAC concentration. It can be observed in Figure 3, that the highest reflectance value was obtained when 20 μL of the *p*-DAC 0.8% (m/v) and 20 μL of the glacial acetic acid were added onto filter paper for reaction with dipyrone.

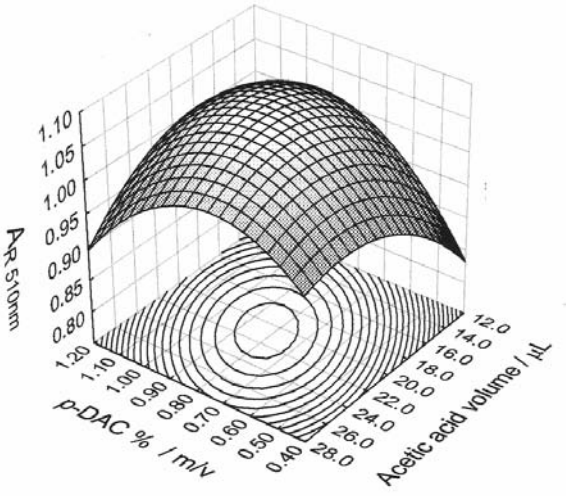


Figure 3. Three-dimensional plot of the optimized surface response of reflectance measurements at variable *p*-DAC concentration and glacial acetic acid volume.

Once the optimal working conditions have been established, the stability of color was evaluated by

Table 2. Design matrix of the central composite design

Run	Un-coded variables levels		Coded variables levels	
	p-DAC % (m/v)[a]	Acetic Acid/(μL)[b]	*p*-DAC % (m/v)[a]	Acetic Acid/(μL)[b]
1	0.6	15	-1	-1
2	1.0	15	1	-1
3	0.6	25	-1	1
4	1.0	25	1	1
5[c]	0.8	20	0	0
6[c]	0.8	20	0	0
7[c]	0.8	20	0	0
8[c]	0.8	20	0	0
9	0.52	20	-1.41	0
10	1.08	20	1.41	0
11	0.8	13	0	-1.41
12	0.8	27	0	1.41

[a] The volume spotted was fixed at 20 mL, [b] Glacial acetic acid (99%), [c] Center points in quadruplicate

following the color development at ambient temperature (25 ± 2 °C). It was observed that the reflectance measurement remained stable for at least 20 hours at room temperature.

Analytical data

The developed analytical method was validated by evaluating linear dynamic range, precision, limit of detection (LOD) and limit of quantification (LOQ) as well as by applying standard addition technique.

Reflectance spectrophotometric methods of analysis usually involve the use of a calibration curve prepared by measuring the reflectance of samples containing known amounts of the substance of interest. Reflectance studies can be used for quantitative chemical analysis in much the same way that transmission spectrometry is used. In reflectance analysis, the optical density for reflectance measurements is $A_R = - \log T_R$, analogous to absorbance, where $T_R = I / I_0$ is the reflecting power, I_0 being the intensity of incident radiant energy and I the intensity of that reflected by the medium.[24,29]

The most widely accept theory of diffuse reflectance is that developed by Kubelka- Munk.[24,29,36] The Kubelka-Munk function, $F(T_R)$, is defined as $F(T_R) = (1-T_R)^2/2T_R$, where T_R is the percent reflection measured with respect to a standard white. $F(T_R)$ is related to analyte concentration by $F(T_R) = \varepsilon C/s$, where ε is the molar absorptivity, C the concentration of the analyte, and s is the scattering coefficient of the sample surface. By assuming the absorptivity and scattering coefficient of the sample of our surface are constant at a given wavelength, $F(T_R)$ can therefore be related directly to analyte concentration. As in a solution system which obeys the Beer-Lambert law, adherence to this form of the Kubelka-Munk equation is indicated by linearity of a calibration curve. For quantitative measurements, the literature describes many types of plots relating signal and concentration.[22-30]

As an aid to the choice of an optimum concentration range for the reflectance measurements, the reflectance values for standards may be plotted as a logarithmic function of concentration. The curve is similar to a Ringbom plot for solution measurements. The linear portion indicates the optimum concentration range. The Ringbom method has the advantage of not only making the optimum range and maximum accuracy, but also of providing a plot usable as a calibration curve.

In our study, a linear relationships was observed between A_R (optical density for reflectance measurements at 510 nm) and log C, where C = [dipyrone] 10^3 mol L^{-1} (the factor 10^3 was used to adjust the calibration graph to log values over zero). Under the optimized experimental conditions, the linear calibration curve was constructed from 1.42×10^{-4} up to 2.85×10^{-3} mol L^{-1} dipyrone standard solutions. The least square treatment of calibration data (n = 9) yielded the regression equation: $A_R = 2.17 \times 10^{-2} (\pm 1.25 \times 10^{-2}) + 6.78 \times 10^{-1} (\pm 1.17 \times 10^{-2})$ *C*. The correlation coefficient was 0.999, indicating the excellent linearity of the calibration curve at 95% confidence level.

Assay precision was defined by determining intraday and interday variation, expressed as relative standard deviation (RSD). The interday variation was evaluated over 5 days. The intraday precision and interday precision were studied for 10 replicate analyses of 7.90×10^{-4} mol L^{-1} dipyrone solution. The coefficients of variation were 1.1 and 0.9%, respectively. The LOD (3.SD^{blank}/slope of analytical curve) and LOQ (10.SD^{blank}/slope of analytical curve) were 1.20×10^{-5} mol L^{-1} and 4.00×10^{-5} mol L^{-1}, respectively.[37]

In order to investigate the presence of matrix effects on the proposed method, a recovery study was carried out. In this study, 3.98×10^{-4} mol L^{-1}; 7.97×10^{-4} mol L^{-1} and 1.20×10^{-3} mol L^{-1} of dipyrone reference solutions were added in four selected pre-analyzed pharmaceutical preparations. The results presented in Table 3 reveal the absence of significant matrix effects on the reflectometric measurements.

Table 3. Recovery data for dipyrone spiked in pharmaceutical formulations

Samples	Added / (mol L^{-1})	Found / (mol L^{-1})	Recovery (%)[a]
Liquids			
A	0.00	8.00×10^{-4}	—
	3.98×10^{-4}	1.20×10^{-3}	100.5
	7.97×10^{-4}	1.60×10^{-3}	100.4
	1.20×10^{-3}	2.01×10^{-3}	100.8
			μ^a = 100.6 ± 0.2
B	0.00	7.94×10^{-4}	—
	3.98×10^{-4}	1.19×10^{-3}	99.5
	7.97×10^{-4}	1.60×10^{-3}	101.1
	1.20×10^{-3}	2.00×10^{-3}	100.8
			μ^a = 100.5 ± 0.9
Tablets			
C	0.00	8.01×10^{-4}	—
	3.98×10^{-4}	12.0×10^{-3}	100.3
	7.97×10^{-4}	1.60×10^{-3}	101.5
	1.20×10^{-3}	2.00×10^{-3}	101.7
			μ^a = 101.2 ± 0.8
D	0.00	7.98×10^{-4}	—
	3.98×10^{-4}	1.21×10^{-3}	103.5
	7.97×10^{-4}	1.60×10^{-3}	100.6
	1.20×10^{-3}	2.04×10^{-3}	103.3
			μ^a = 102.5 ± 1.6

[a]Average ± standard deviation (SD) for the three determinations

Study of interferences

The effects of the usual excipients and associated drugs commonly present in commercial pharmaceutical formulations involving dipyrone were carefully examined. The concomitants studied were lactose, sucrose, citric acid, starch, sodium saccharin, sodium sulphite, sodium benzoate, talc, magnesium stearate, polyvinylpirrolidone, sorbitol, methylcellulose, caffeine, Aspirin®, acetaminophen, ascorbic acid, phenacetin, oxyphenbutazone, acid promethazine hydrochloride, adiphenine hydrochloride, butylscopolamine bromide, salycilamide and phenobarbital. For this study, solutions containing dipyrone (250 μg mL^{-1} or 7.11×10^{-4} mol L^{-1}) and each one of the concomitants taken separately in concentrations equal or 10 times greater than that of dipyrone were shaken with deionized water in a magnetic mixer for 5 min, diluted, filtered where necessary, and analyzed under the same conditions described in the recommended procedure.

The effect of each concomitant was considered to be interference when the signal showed an error over or equal to 3.0% in the determination of the drug. No interferences were observed in the presence of the substances tested. The percentage recoveries of dipyrone varied between 97.0 and 102.1% with the relative standard deviation ranged from 0.1 to 2.8%, as shown in Table 4.

Pharmaceutical compounds with primary or secondary aromatic amino groups such as mefenamic acid, diclofenac sodium, metoclopramide hydrochloride, aceclofenac, etodolac, isoniazid, glafenine, metolazone, hydrochlorothiazide, furosemide, chlortalidone, bendroflumethiazide, procaine and benzocaine does not reacted with *p*-DAC in acid medium (glacial acetic acid) at room temperature (25 °C). Moreover, these substances are seldom included in dosage forms comprising dipyrone.

The lack of interference from aspirin, acetanilide, aceclofenac, etodolac, glafenine, phenacetin, salicylamide, oxyphenbutazone and acetaminophen is noteworthy because all of these drugs are mild analgesics as well as antipyretics, and some these are cheaper than dipyrone (much cheaper, in the case of Aspirin®, phenacetin and acetaminophen). Falsification and/or adulteration involving the total or partial replacement of dipyrone by any one of these drugs can, therefore, be readily detected by the proposed method.

Analytical application

The applicability of the proposed method for the determination of dipyrone in commercial dosage forms was examined by analyzing marketed products. The

Table 4. Study of interferences

Excipients	Dipyrone:Excipient [a]		Dipyrone:Excipient [b]	
	Recovery (%) [c]	R.S.D.	Recovery (%) [c]	R.S.D.
Magnesium stearate	98.0 ± 0.9	0.9	98.5 ± 0.1	0.1
Starch	98.5 ± 0.1	0.1	97.8 ± 1.2	1.2
Talc	98.5 ± 1.5	1.5	100.5 ± 0.9	0.9
Sodium saccharin	97.7 ± 2.0	2.0	101.1 ± 2.0	2.0
Sodium bisulfite	97.0 ± 1.0	1.0	97.8 ± 1.9	2.0
Sucrose	101.1 ± 1.9	1.9	98.4 ± 2.3	2.3
Lactose	97.8 ± 1.9	1.9	98.2 ± 2.6	2.6
Sorbitol	98.6 ± 2.3	2.3	98.4 ± 2.8	2.8
Caffeine	102.0 ± 1.7	1.7	97.9 ± 1.8	1.8
Aspirin®	100.2 ± 0.8	0.8	100.7 ± 0.6	0.6
Ascorbic acid	99.0 ± 0.8	0.8	101.0 ± 1.8	1.8
Acetaminophen	101.2 ± 0.8	0.8	100.9 ± 0.5	0.5
Phenacetin	101.8 ± 0.7	0.7	99.2 ± 0.8	0.8
Acetanilide	101.1 ± 0.6	0.6	99.9 ± 0.9	0.9
Oxyphenbutazone	100.2 ± 1.0	1.0	101.2 ± 1.2	1.2
Promethazine hydrochloride	98.5 ± 0.5	0.5	100.4 ± 1.4	1.4
Adiphenine hydrochloride	100.2 ± 1.3	1.3	101.4 ± 0.8	0.8
n-Butylscopolamine bromide	99.2 ± 1.5	1.5	100.7 ± 0.8	0.8
Salicylamide	101.9 ± 0.5	0.5	101.2 ± 0.9	0.9
Phenobarbital	99.0 ± 0.6	0.6	100.2 ± 0.3	0.3
Polyvinylpirrolidone	98.8 ± 2.1	2.1	100.9 ± 1.6	1.6
Citric acid	100.0 ± 0.6	0.7	98.5 ± 2.2	2.2
Sodium benzoate	102.1 ± 1.9	1.8	99.3 ± 1.4	1.4
Methylcellulose	99.0 ± 0.8	0.8	98.3 ± 0.1	0.1

[a] Dipyrone 250 mg mL^{-1} and Excipient 250 mg mL^{-1}, [b] Dipyrone 250 mg mL^{-1} and Excipient 2500 mg mL^{-1}, [c] Average ± standard deviation (SD) for the three determinations.

Table 5. Dipyrone determination in pharmaceutical formulations

Samples	Label values	Proposed method			Reference Method [8]
		Found[c]	*t* value (2.78)[d]	*F* value (19.00)[d]	Found[c]
Tablets[a]					
A	500	500 ± 4	0.06	2.56	500 ± 3
B	320	321 ± 4	0.22	3.06	320 ± 2
C	500	496 ± 4	0.74	2.56	494 ± 2
D	500	506 ± 2	1.07	2.25	504 ± 3
E	500	521 ± 2	1.43	4.00	518 ± 3
F	250	245 ± 3	0.93	1.69	245 ± 3
Solutions[b]					
G	500	499 ± 3	0.26	1.00	499 ± 3
H	333	337 ± 1	0.42	2.25	337 ± 3

[a] Label values for tablets: mg tablet^{-1}, [b] Label values for solutions: mg mL^{-1}, [c] Average ± standard deviation (SD) of three independent analysis, [d] The values between parentheses are the theoretical values of *t* and *F* at 95% confidence level.

results of the proposed method were statistically[38] compared with those obtained by the Brazilian Pharmacopoeia procedure[8] and are summarized in Table 5. In all cases, the calculated *t* and *F* values did not exceed the theoretical values at 95% confidence level, indicating that there is no significant difference between either method concerning precision and accuracy in the determination of dipyrone in pharmaceutical preparations.

Conclusions

In the present study, it was demonstrated the potential of the proposed reflectometric method for the analysis of dipyrone in pharmaceutical preparations. The developed method is an advantageous alternative to other available methods, because it is simple, rapid, portable, environmentally friendly (requires extremely low consumption of reagents/solvents) and does not involve specific or complicated sample treatments.

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