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Short Communication

Spectrophotometric determination of dipyrone in pharmaceutical preparations by using chromotropic acid

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Dedicated to the memory of Professor Waldemar Saffioti (1922–1999)

Abstract

A spectrophotometric method for the determination of dipyrone in pharmaceutical preparations is proposed. This method is based on selective oxidation of dipyrone, in the presence of sulphuric acid, splitting off formaldehyde which reacts with chromotropic acid, also in a sulphuric acid medium, producing a violet–red compound (λ_{max} 575 nm). Beer's law is obeyed in a concentration range of 0.57–5.7 ppm dipyrone with an excellent correlation coefficient ($r = 0.9997$). The results show a simple, accurate, selective and readily applied method to the determination of dipyrone in pharmaceutical products. The analytical results obtained for these products by the proposed method are in agreement with those of the Brazilian Pharmacopoeia procedure. No interference was observed from common excipients in formulations. Recoveries were within 98.7–101.2%, with standard deviations ranging from 0.2 to 1.7%.

Keywords: Dipyrone; Chromotropic acid; Spectrophotometric determination; Pharmaceutical preparations

1. Introduction

Dipyrone (sodium salt of 1-phenyl-2,3-dimethyl-4-methylaminomethane sulphonate-5-pyrazolone; analgin, novalgin) is widely used as an analgesic and antipyretic drug. Because of its importance, considerable work has been done on its detection and quantification. Most of the methods used for the determination of this drug include titrimetry in aqueous [1,2] and non-aqueous [3] media, potentiometry [4], coulometry [5], polarography [6], TLC [7], HPLC with UV detection [8], fluorimetry [9] and spectrophotometry [7,10–45].

Molecular absorption spectrophotometry is by far the instrumental technique of choice in industrial laboratories, owing mainly to its simplicity, often demanding low-cost equipment and lending itself to easy automation of trace analysis procedures.

As already mentioned, a number of spectrophotometric methods for dipyrone determination have been reported. Almost all these methods present significant limitations and drawbacks. Thus, those based on UV absorption [10–21] present low selectivity, as all unsaturated compounds display one or more bands (often broad ones) in that region of the spectrum. Their application is restricted to one- [13,14], two- [10–12,15,17,18,20], three- [16,19], or four-component [21] systems, in synthetic mixtures [11,12,15,17–21] and to very simple pharmaceutical preparations comprising only one- [14], two- [10,17,20] or three-active components [16]. It has been stated that even for two-component mixtures best selectivity is achieved only after TLC separation [15]. Complex samples usually require chemical processing prior to the photometric assay. During this step, ill-defined yellow coloured substances are

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often produced. These seriously interfere in some of the proposed methods [28,36,38,40,42,44], which recommend absorbance measurements at 350–435 nm, unless such substances are previously removed. Classical oxidising agents attack dipyrone [22–31] and, likewise, many other important components of pharmaceutical formulations, yielding colour reactions which are very similar to that provided by dipyrone [46–48]. As expected, many interferences have been noted [24–27] and these methods are best regarded as useful for determining pharmacological reductants [24,27]. Organic bases, e.g. amines, quaternary ammonium salts and heterocyclic compounds have a tendency to form chloroform extractable ion pairs with dyes; this property has been exploited for the assay of several drugs [49], including dipyrone [27,32,33]. However, the proposed procedures [27,32,33] are very prone to interferences and these have indeed been reported [27,32].

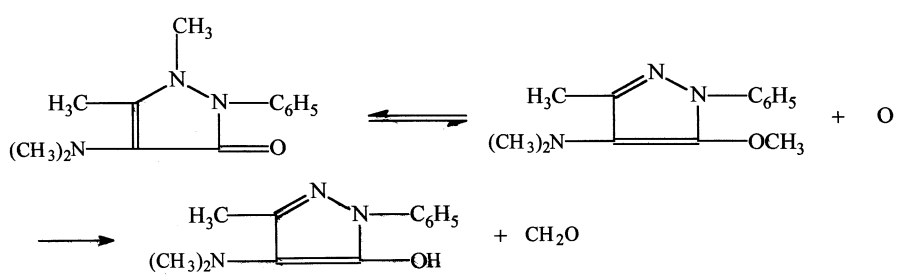
In an endeavour to overcome most of the interfering substances, separation procedures such as time consuming precipitation [20,41] and chromatographic conditioning [7,8,15], tedious and troublesome solvent extraction [12,27,33,38] as well as a previous oxidation step [12] have been coupled to some of the established methods. Low sensitivity [30,44] and low precision [7,28,29] are reported. Particularly sensitive direct [10,15,17,20,26–28,34,35,38,42,43] and indirect [22–25] methods have been proposed; some are inherently unselective [10,15,22–27,38]; others [17,20,28,34,35,42,43] lack proper selectivity, especially in connection with the determination of dipyrone in multicomponent samples, comprising related drugs. It is perhaps worth noting that methods employing reactions with 1,2-naphthoquinone-4-sulphonate [50] and 4-dimethylaminocinnamaldehyde [51] were presented for estimating other pyrazolone pharmaceuticals in dosage forms, i.e. phenylbutazone [50] and oxyphenbutazone [50,51]. The experimental conditions adopted in these methods are closely related to those applied to determine dipyrone by using the aforementioned chromogenic reagents [34,35,43]. On the other hand, many of the proposed methods [11,13,15,18,21,25,26,32,34,44] have not been applied to pharmaceutical formulations and some [13,25,32,34,44] not even to synthetic mixtures or simulated dosage forms, thus precluding the assessment of their usefulness in real analysis.

From the above considerations, the need for a fast, low-cost and selective method seems clearly apparent, especially for routine quality control analysis of pharmaceutical products containing dipyrone. In the search for such a method, our attention was attracted to a spot test for pyramidone (a dipyrone analogue; 1-phenyl-2,3-dimethyl-4-dimethylamino-5-pyrazolone) described by Feigl [52], which is based on a very selective oxidation of that compound, in the presence of sulphuric acid, splitting out formaldehyde. The reducing action of pyramidone is related to its tendency to tautomerise [53]; the oxidation probably begins with the isomeric methoxy form [52] of the pyrazolone (Scheme 1).

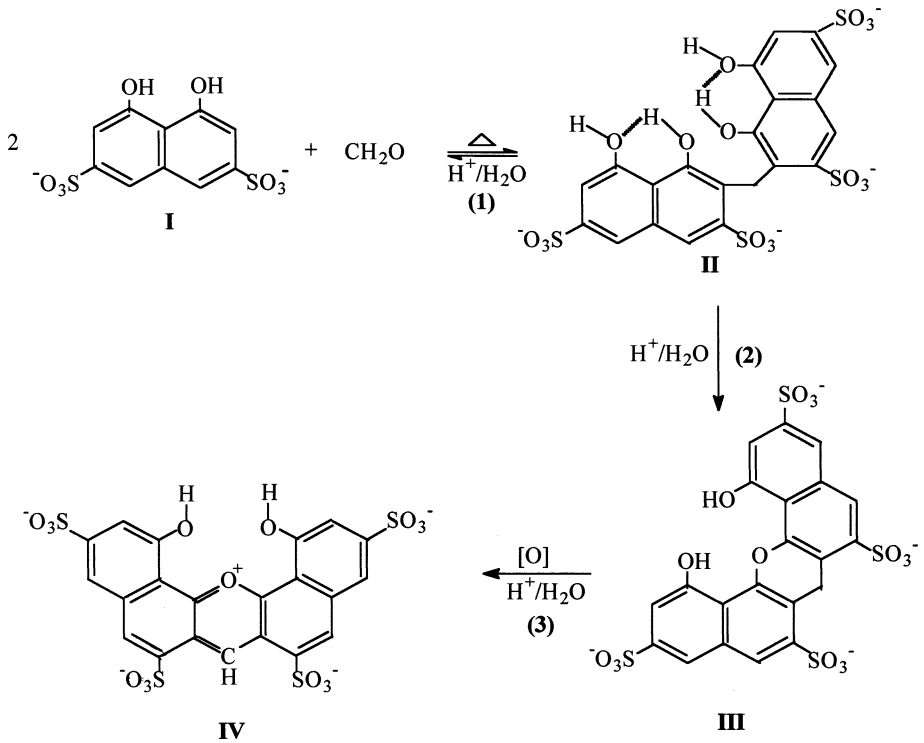
The formaldehyde, once formed, is identified by warming it with chromotropic acid (**I**), also in sulphuric acid solution, yielding a soluble violet–red colour [52]. The nature of this chromogen has never been unambiguously proven but recent experimental evidence [54] supports the hypothesis that it has a mono-cationic dibenzoxanthylium structure (**IV**), formed as shown in Scheme 2.

Sulphuric acid participates in steps (1) to (3); sensitivity increases with increasing acid concentration [54]; maximum effectiveness is attained with concentrated (18 M) sulphuric acid [52]. This test was first developed into a quantitative spectrophotometric method for dipyrone in this laboratory [55] by using 15 M sulphuric acid.

In the analysis of 'Sedorga' tablets and liquid (products manufactured and marketed in Brazil by Bristol Laboratories Inc.) which contained, in addition to dipyrone, hydrochlorides of papaverine and adiphenine, homatropine methylbromide, starch, lactose, arabic gum, magnesium stearate, FDC dye yellow no. 5, sodium sulphite, ethanol and anise essence, by the originally established method [55], some interferences were noted. Afterwards, Mucciarelli and Aschieri [56] also observed interaction of chromotropic acid with several substances of pharmacological interest by working with 13.8 M H_2SO_4.



Scheme 1.



Scheme 2.

The work described in this paper was undertaken to develop an improved method for dipyrone estimation, using chromotropic acid as chromogenic reagent, by optimising the reaction conditions so as to determine the analyte either in pure form or in a wide diversity of commercial pharmaceutical formulations, without the need of previous separation procedures.

In this method the interferences earlier noted [55] were stepwise circumvented by reducing progressively the sulphuric acid concentration and almost no interference took place with 9.3 M H_2SO_4 in the final reacting system.

2. Experimental

2.1. Instruments

A Cary 1E spectrophotometer with 1 cm matched silica cells was used for all absorbance measurements. Volume measurements were made with digital 'Brand' plunger-operated pipetter (25–250 μl). All experiments were performed in a thermostated room (25 ± 1)°C.

2.2. Reagents

For the preparation of the solutions and samples, deionised water and grade A glassware were used throughout. Analytical-reagent or pharmaceutical grade chemicals were used.

- Sulphuric acid solution: 11.2 M. Prepared in the usual way, from the concentrated acid (96%).
- Chromotropic acid (disodium salt dihydrate, $C_{10}H_6O_8S_2Na_2{\cdot}2H_2O$): a 20% (m/v) aqueous solution was freshly prepared.
- Standard dipyrone solution ($C_{13}H_{16}N_3NaO_4S{\cdot}H_2O$): A 0.285 mg/ml stock solution of dipyrone (based on the anhydrous compound) was prepared by dissolving 0.0750 g of the drug in 250 ml of deionised water. Working standard solutions were obtained by appropriate dilution of this stock solution with the same solvent.

3. Recommended procedure

3.1. Calibration curve

Transfer 500 μl of dipyrone working standard solutions (comprising 28.5–285 ppm of the drug) into test tubes with polished glass stoppers. Add to each tube 500 μl of 20% chromotropic acid followed by 5.0 ml 11.2 M H_2SO_4 (under stirring). The tubes are loosely stoppered and heated for 25 min in a steam bath (100°C). Afterwards, they are cooled at 25°C. The solutions are quantitatively transferred into 25 ml standard flasks and the volume completed with deionised water. The blank solution is prepared in a similar way, but omitting dipyrone. Record the absorbances at 575 nm, against the reagent blank. Calibration graphs are

prepared by plotting absorbance against drug concentration. These graphs or the corresponding linear least squares equations are used to convert absorbance into dipyrone concentration, for any analysed sample.

3.2. Analysis of formulations

3.2.1. Tablets

Six tablets were finely powdered. A sample equivalent to one-eighth of the mass of each tablet was weighed accurately and transferred into a 500 ml standard flask and the volume completed with deionised water. Aliquots of 500 μl of this solution were analysed according to the recommended procedure.

3.2.2. Solutions

For the analysis of these solutions, 500 μl of each solution was transferred into a 1000 ml standard flask and diluted to the mark with deionised water. Aliquots of 500 μl of this diluted solution were taken for analysis, following the recommended procedure.

4. Results and discussion

The absorption spectrum of the reaction product (Fig. 1) shows that the best analytical wavelength is located at 575 nm.

Variable parameters affecting dipyrone oxidation and the coupled colour reaction with chromotropic acid were investigated. Experimental evidence [52,55] shows, in compatibility with the reactions suggested in Scheme 2, that maximum sensitivity is reached with concentrated sulphuric acid. On the other hand, tolerance toward interferences is less in that condition, as previously pointed out [55,56] and confirmed in this work. The best compromise between sensitivity and selectivity was found by developing the reactions in 9.3 M H_2SO_4, as described in the recommended procedure. Lack of interference from common excipients and active drugs, especially those often associated with dipyrone formulations, advantageously outweigh sensitivity reduction as dipyrone usually appears in relatively high concentrations as a component of solid and liquid dosage forms (i.e. 250–500 mg/tablet and 300–500 mg/ml).

The adopted chromotropic acid concentration was found to be sufficient for providing maximum and reproducible colour intensity. The data given in Table 1 show that a heating time of 25 min at 100°C is required for full colour development and the resulting chromogen is stable for at least 3 days at room temperature. No colour was developed at 25°C. Beer's law is obeyed within 0.57–5.7 ppm of drug, in the final solution, with an excellent correlation coefficient ($r = 0.9997$; slope = 0.10885 ± 0.00093 ml/μg per cm and intercept nearly zero).

The possible interference of excipients, additives, diluents, flavouring agents and associated drugs commonly present in commercial pharmaceutical formulations involving dipyrone was investigated. It has been found that talc, starch, lactose, sucrose, gelatin, arabic gum, sodium sulphite, ethanol, magnesium stearate, carnauba wax, white wax, titanium dioxide, polyethylene glycol, anise essence, antipyrine, caffeine, hydrochlorides of adiphenine and papaverine, homatropine methylbromide, promethazine and isometheptene do not interfere with the determination of dipyrone by the presently proposed method.

In order to assess the utility of the presently developed method it was applied to the estimation of dipyrone in several dosage forms, both solid and liquid. The results, presented in Table 2, compare favourably with the official method of the Brazilian Pharmacopoeia [2] (iodimetric titration). The average recoveries obtained by the proposed method ranged from 98.7 to 101.2% for the

Table 1
Effect of heating time (100°C) on the reaction [a]

Heating time (min)	Absorbance [b]
5	0.341
10	0.448
15	0.483
20	0.526
25	0.560
30 [c]	0.560

[a] Dipyrone concentration: 5.7 ppm.
[b] Measurements taken at 575 nm against the reagent blank for reactants after heating at 100°C, followed by cooling and dilution (as described in the recommended procedure).
[c] The absorbance remains unchanged after standing for 3 days at 25°C.

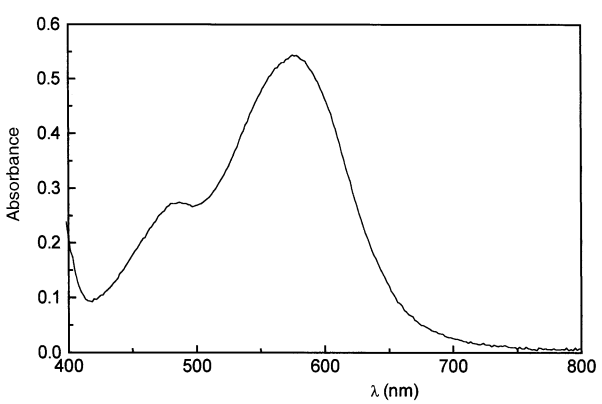


Fig. 1. Absorption spectrum of the reaction product. Dipyrone final concentration = 5.1 ppm; optical path = 1 cm. Measurements taken at 25°C against the reagent blank after heating for 25 min at 100°C, cooling and diluting, as described in the recommended procedure.

Table 2
Determination of dipyrone in commercial pharmaceutical preparations [a]

Sample	Manufacturer	Label to content	Proposed method		Official method [2]	
			Found [b]	Recovery (%) [b]	Found [b]	Recovery (%) [b]
Tablets [c]						
Anador	Boehringer De Angeli	500	499 ± 1	99.8 ± 0.8	502 ± 1	100.4 ± 0.9
Baralgin	Sarsa	500	497 ± 2	99.4 ± 0.4	496 ± 2	99.2 ± 0.4
Buscopan	Boehringer De Angeli	250	247 ± 2	98.8 ± 0.9	254 ± 1	101.6 ± 1.3
Cefaliv	Aché	350	351 ± 1	100.3 ± 0.8	345 ± 2	98.6 ± 0.6
Conmel	Sanofi Winthrop	320	322 ± 1	100.6 ± 0.9	318 ± 2	99.4 ± 1.2
Doralgin	Dorsay	300	299.5 ± 1.3	99.8 ± 1.2	301 ± 1	100.3 ± 0.9
Fluviral	Biolab/Searle	250	253 ± 1	101.2 ± 0.8	252.5 ± 1.1	101 ± 1
Lisador	Farmasa	500	499 ± 1	99.8 ± 0.9	500 ± 1	100 ± 1
Magnopyrol	Abbott	500	500 ± 1	100 ± 1	500 ± 1	100 ± 1
Nevralgina	Abbott	500	501 ± 1	100.2 ± 0.8	501 ± 1	100.2 ± 0.9
Novalgina	Hoechst	500	496 ± 1	99.2 ± 0.2	501 ± 1	100.2 ± 0.5
Par	Sanofi Winthrop	500	500.5 ± 1.7	100.1 ± 1.3	500 ± 1	100 ± 1
Solutions [d]						
Dorflex	Merrel Lepettit	300	303 ± 2	101 ± 1	297.5 ± 1.6	99.2 ± 1.2
Lisador	Farmasa	333	337 ± 2	101.2 ± 1.7	336 ± 1	100.9 ± 1.3
Magnopyrol	Abbott	400	408 ± 1	102 ± 1	398.5 ± 1.7	99.6 ± 1.1
Neosaldina	Knoll	300	296 ± 2	98.7 ± 0.6	303 ± 1	101 ± 1
Nevralgina	Clímax	500	505 ± 1	101 ± 2	499 ± 1	99.8 ± 0.8
Toloxin	Biolab	400	402 ± 1	100.5 ± 1.7	401 ± 1	100.3 ± 1.6

[a] These determinations refer to the anhydrous drug.
[b] Average ± SD of six determinations, performed within 3–4 days.
[c] Label to content for tablets: mg/tablet.
[d] Label to content for solutions: mg/ml.

analysed drug; the SDs were within 0.2–1.7%, indicating very good accuracy and precision. The mentioned advantages of the method, rank it as rather competitive, compared with the existing spectrophotometric methods [7,10–45] and thus suggest its use as an alternative to pharmacopoeial procedures in the routine quality control of pharmaceutical preparations comprising dipyrone.

Preliminary experiments have shown that the reactions which form the basis of the presently developed procedure can also be successfully carried out on a silica thin-layer plate. Appropriate heating has been provided by a hair-dryer. It has also been found that the silica surface exerts a catalytic effect on the reaction since partial colour development is observed even at room temperature. These results suggest the possibility of performing quantitative spot test analysis via reflectance measurements along the lines recently established by Tubino et al. [57].

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