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Short Communication

Spectrophotometric methods for the determination of ritodrine hydrochloride and its application to pharmaceutical preparations

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Abstract

Two simple and sensitive spectrophotometric methods are described for the determination of ritodrine hydrochloride (RTH) in both pure and dosage forms. The methods are based on the interaction of diazotised *p*-nitroaniline (DPNA) and sulphanilic acid (DSNA) with RTH in an alkaline medium. The resulting azo dyes are measured at 480 nm (for the DPNA method) and at 440 nm (for the DSNA method) and are stable for more than 1 h. The optimum reaction conditions and other analytical parameters are evaluated. A study of the effect of commonly associated excipients and additives do not interfere with the determinations. Statistical analysis of results indicates that the methods are precise and accurate.

Keywords: Ritodrine hydrochloride; Spectrophotometric determination; Pharmaceutical formulations; Drug analysis

1. Introduction

Ritodrine hydrochloride (RTH), 1-(4-hydroxy phenyl)-2-[2-(4-hydroxy phenyl)ethyl amino] propanol, is a β_2-sympathomimetic amine used to arrest preterm delivery in pregnant women [1]. The pharmacokinetics of ritodrine in pregnant women require detailed characterisation in order to establish whether the present intravenous infusion regimen is the most appropriate to rapidly achieve therapeutic plasma concentrations while minimising significant maternal side effect such as tachycardia. RTH is used widely in obstetrics [2]. In view of the increased pharmaceutical applications of ritodrine, its assay and quality control are very important. Only very few methods are reported in the literature for this purpose. The important analytical methods recommended for the assay of ritodrine are those based on spectrophotometry [3,4], fluorimetry and spectrophotometry [5] and HPLC [6]. The current United States Pharmacopoeia (2000) [7] and British Pharmacopoeia (1998) [8] methods for the analysis of RTH in pharmaceutical formulations are based on HPLC. The present paper describes two facile, sensitive and accurate methods for the determination of RTH using diazotised *p*-nitroaniline (DPNA) and diazotised sulphanilic acid (DSNA) in an alkaline medium. The proposed methods have been applied to the assay of RTH in tablets and injection.

2. Experimental

2.1. Apparatus

All spectral measurements were carried out with a JASCO model UVIDEC–610 and Elico model CL-27 digital spectrophotometers with 1-cm matched cells.

2.2. Reagents

All chemicals were of analytical reagent grade.

DPNA solutions (0.2%) — prepared by dissolving 50 mg of *p*-nitroaniline in 3 ml of concentrated hydrochloric acid, cooled and 1 ml of 2% sodium nitrite solution was added. After 5 min, 1 ml of 5% sulphamic acid was

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added to remove the excess of nitrite and diluted to 25 ml with water. The solution was mixed well and kept in an ice bath. This reagent should be used within 5 h.

DSNA solution — prepared by mixing 40 ml of sulphanilic acid solution (1%) in 1 M hydrochloric acid and 20 ml of sodium nitrite solution (2%). The excess of nitrite could be removed by the addition of 1 ml of sulphamic acid solution (5%). This reagent should be used within 1 h after preparation.

2.3. Standard solution

Aqueous solution of ritodrine hydrochloride (RTH, Duphar-Interfran Ltd, Mumbai, India) was prepared by dissolving 100 mg of the sample in 100 ml of distilled water. The working solution was prepared as required by dilution.

2.4. General procedure

DPNA method: aliquots of the standard solution (0.5–4 ml, 50 μg/ml) were transferred into a series of 25 ml standard flasks. A volume of 3 ml of 0.2% DPNA solution and 4 ml of 5% sodium hydroxide solution were added to each flask. The contents were diluted to the mark with distilled water and mixed well. After 10 min, the absorbance of the solution was measured at 480 nm against reagent blank.

DSNA method: aliquots of the standard solution (0.5–4 ml, 100 μg/ml) were transferred into a series of 25 ml standard flasks. A volume of 5 ml of DSNA solution and 4 ml of 5% sodium hydroxide solution were added to each flask. The contents were diluted to the mark with distilled water and mixed well. After 10 min, the absorbance of the solution was measured at 440 nm against reagent blank. A calibration graph was drawn and the regression equation calculated.

2.5. Procedure for pharmaceutical formulations

A quantity of the sample equivalent to 25 mg of the drug was weighed accurately and transferred into a 100 ml standard flask and the volume made up with distilled water (the sample was thoroughly shaken for about 30 min) and then filtered. Appropriate aliquots of the drug solution were taken and the general procedure was followed for analysing the drug content.

For the analysis of injection solution, the requisite volume was transferred to a 100-ml standard flask and diluted to the mark with distilled water. The drug content in the diluted solution was determined as described above. The results of the analysis are given in Tables 1 and 2.

3. Results and discussion

The methods are based on the reaction between RTH and DPNA or DSNA in an alkaline medium to produce an orange-yellow coloured species with maximum absorption at 480 nm (for DPNA) and at 440 nm (for DSNA). The absorption spectra of the azo dyes are given in Fig. 1. The reaction between RTH and DPNA or DSNA revealed a 1:2 molar ratio (drug to reagents), as illustrated in Fig. 2.

Table 1
Analysis of ritodrine hydrochloride in various dosage forms

Methods	Preparation	Within-day			Between-day		
		Analyte taken (μg/ml)	Analyte [a] found (μg/ml) ± SD	CV%	Analyte taken (μg/ml)	Analyte [a] found (μg/ml) ± SD	CV%
DPNA	Yutopar tablet	2	1.99 ± 0.033	1.66	2	1.97 ± 0.034	1.73
		4	3.98 ± 0.066	1.65	4	3.89 ± 0.046	1.18
		6	5.99 ± 0.094	1.57	6	5.92 ± 0.031	0.52
	Yutopar injection	2	1.99 ± 0.078	3.92	2	1.96 ± 0.043	2.19
		4	3.98 ± 0.082	2.06	4	3.91 ± 0.046	1.18
		6	6.01 ± 0.041	0.68	6	5.99 ± 0.016	0.27
DSNA	Yutopar tablet	4	3.99 ± 0.025	0.63	4	3.90 ± 0.046	1.18
		8	7.98 ± 0.029	0.36	8	7.94 ± 0.041	0.52
		12	12.05 ± 0.032	0.27	12	11.95 ± 0.031	0.26
	Yutopar injection	4	4.01 ± 0.034	0.85	4	3.98 ± 0.027	0.68
		8	7.99 ± 0.025	0.31	8	7.94 ± 0.048	0.60
		12	11.96 ± 0.035	0.29	12	11.92 ± 0.041	0.34

[a] Average of five determinations.

Table 2
Comparison between the proposed and reference methods

Methods	Preparation	Label claim (mg)	% Recovery [a] ± SD		*t*-value [b]	*F*-value [c]
			Reference method [5]	Proposed method		
DPNA	Yutopar tablet	10	100.2 ± 0.5	99.5 ± 0.5	2.59	1.00
	Yutopar injection	50/10 ml	99.9 ± 0.4	99.6 ± 0.5	0.88	1.56
DSNA	Yutopar tablet	10	100.01 ± 0.5	99.5 ± 0.6	2.57	1.44
	Yutopar injection	50/10 ml	100.5 ± 0.4	99.9 ± 0.5	2.38	1.56

[a] Average of five determinations.
[b] Tabulated value 2.78.
[c] Tabulated value 6.39.

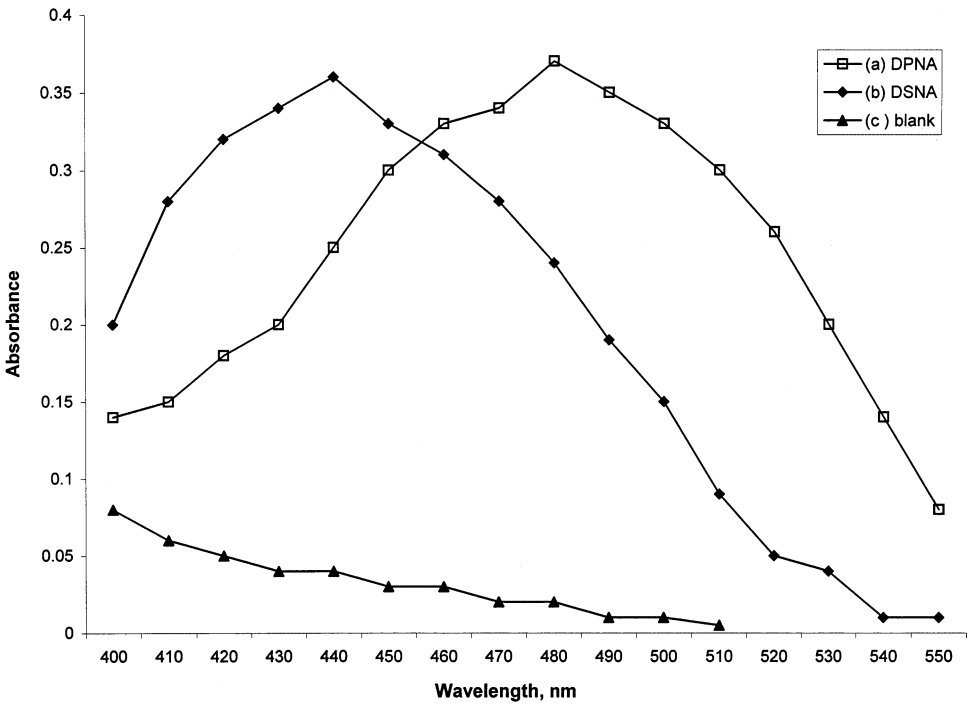

Fig. 1. Absorption spectra of the reaction product of RTH with (a) DPNA, (b) DSNA, and (c) blank; [RTH] = 4 ppm in each instance.

To establish the optimum conditions for the determination of RTH, the effect of several experimental variables were studied and are reported below.

3.1. Effect of alkali

The optimum concentration of sodium hydroxide solution leading to a maximum colour stability was found to be 4 ml of 5% solution in a total volume of 25 ml of the reaction mixture (for both the methods). Higher concentration of base had no effect on colour intensity (Fig. 3).

3.2. Effect of reaction time

The maximum colour intensity was obtained after 10 min, at room temperature (ca. 25 ± 5°C) in both the methods. The colour was stable for a period of 70 min for DPNA and 60 min for DSNA.

3.3. Optical characteristics

Beer's law ranges, molar absorptivity, slope, intercept, correlation coefficients, detection limit and quanitiation limits are presented in Table 3.

3.4. Effect of excipients

To test the accuracy of the methods, recovery experiments were performed on synthetic mixtures of RTH with talc, starch, stearic acid, gum acacia, dextrose and gelatin by the proposed methods and recoveries obtained were in the range 99.8–101.2%.

4. Application

The proposed methods were applied to the quantitative determination of RTH in pharmaceutical formulations. The results in Tables 1 and 2 indicate that the methods give good accuracy and precision, with satisfactory agreement with the results obtained by the reference method.

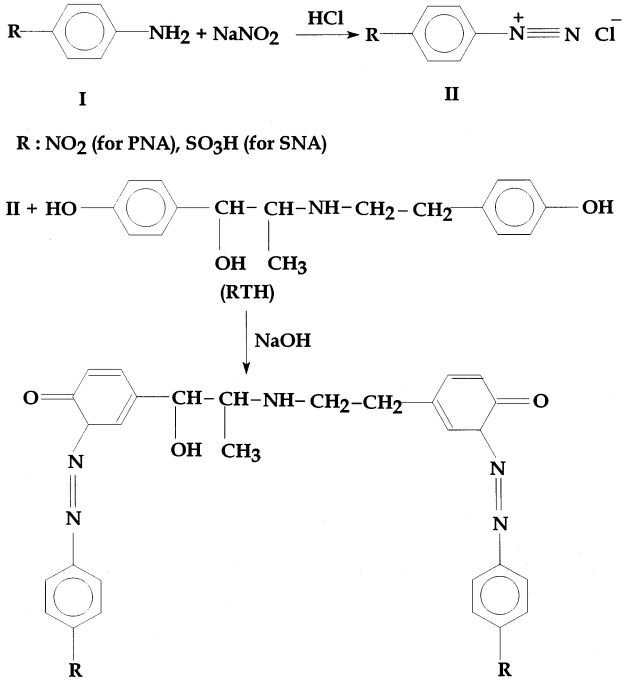

Fig. 2. Proposed mechanism of the reactions of RTH with DPNA and DSNA.

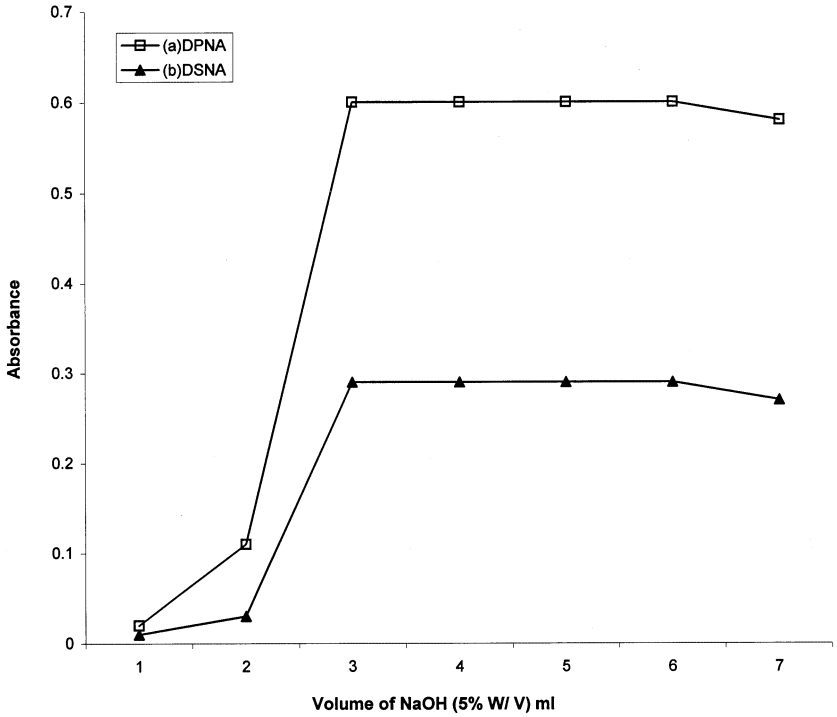

Fig. 3. Effect of NaOH on absorbance of the coloured species; [RTH] = 4 ppm in each instance.

Table 3
Optical characteristics and precision data of RTH

Parameter	DPNA method	DSNA method
Beer's law limit (μg/ml)	1–8	2–16
Molar absorptivity (1 mol/cm)	2.21×10^4	1.34×10^4
Sandell's sensitivity (μg/cm^2 per 0.001 abs unit)	0.015	0.024
Correlation coefficient (r)	0.999	0.999
Regression equation (Y [a])		
Slope (b)	0.058	0.041
Intercept (a)	0.031	0.006
% Relative standard deviation ($n = 7$)	0.065	0.093
Detection limit, D_L (μg/ml)[b]	0.0479	0.0447
Quantitation limit, Q_L (μg/ml)[c]	0.1453	0.1355

[a] $Y = a + bx$, where x is the concentration in μg/ml.
[b] D_L; $3.3\sigma / S$, D_L = detection limit (σ, standard deviation of blank; S, slope of calibration).
[c] Q_L; $10\sigma/S$, Q_L = quantitation limit (σ, standard deviation of blank; S, slope of calibration).

5. Precision

The precision of the proposed methods was evaluated by replicate analysis of samples containing RTH at three different concentrations (low, medium and high) (Table 1). The within day precision showed a CV of 1.66 or 0.63% at low concentration (2 or 4 μg/ml). The between day precision evaluated over a period of five days showed a CV of 1.73 or 1.18% at the low concentration. The low values of both the within and between day CVs at the low concentration reflect the high precision of the proposed methods.

5.1. Accuracy

The results of ritodrine hydrochloride in tablets and injections using the proposed method and reference methods are shown in Table 2. Statistical analysis of the results by t-test and F-test showed no significant difference in accuracy and precision between the proposed and reference methods (Table 2).

6. Conclusions

The paper describes two facile, sensitive and accurate methods for the determination of RTH using diazotised DPNA and DSNA in an alkaline medium. The assay methods do not involve any critical reaction conditions or tedious sample preparation. The proposed methods have been applied to the assay of RTH in tablets and injection.

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