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Original research paper

A sensitive spectrophotometric method for the determination of sulfonamides in pharmaceutical preparations

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A new, simple and sensitive spectrophotometric method for the determination of some sulfonamide drugs has been developed. The method is based on the diazotization of sulfacetamide, sulfadiazine, sulfaguanidine, sulfamerazine, sulfamethazine, sulfamethoxazole, and their coupling with 8-hydroxyquinoline in alkaline media to yield red coloured products with absorption maxima at 500 nm. Beer's law is obeyed from 0.1–7.0 μg mL^{-1}. The limits of quantification and limits of detection were 0.11–0.18 and 0.03–0.05 μg mL^{-1}, respectively. Intraday precision (RSD 0.1– 0.5%) and accuracy (recovery 97.3–100.8%) of the developed method were evaluated. No interference was observed from common adjuvants. The method has been successfully applied to the assay of sulpha drug in pharmaceutical formulations.

Keywords: sulfonamide drugs, diazotization, 8-hydroxyquinoline, spectrophotometry, pharmaceutical formulation

Sulfonamides, important analogues of *p*-amino benzoic acid (1), are used in the treatment of urinary track infections, eye infections and as a prophylaxis of rheumatic fever (2). Antibacterial sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthetase, DHPS, in bacteria. DHPS catalyses the conversion of PABA (*p*-aminobenzoate) to dihydropteroate, a key step in folate synthesis, which is necessary for the cell to synthesize nucleic acids and thus exhibit a bacteriostatic effect (3).

Survey of the literature reveals various methods available for the determination of sulfonamide derivatives. The methods include the nitrite method (4), GC (5), HPLC (6, 7), HPTLC (8), electroanalytical methods (9–12), immune chemical assay (13, 14), spectrofluorimetry (15), differential scanning calorimetry (16), surface enhanced Raman spectrometry (17), spectrophotometry (18–22). Most spectrophotometric methods suffer from low sensitivity, high detection limits, tedious experimental conditions and complex procedures for the preparation of samples or standard solutions.

In the present study, we succeeded in developing a novel coupling agent for sensitive and selective spectrophotometric determination of the sulfonamide class of drugs

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based on the coupling of their diazotized form with 8-hydroxyquinoline (8-HQ), which results in the formation of red coloured products in alkaline medium.

EXPERIMENTAL

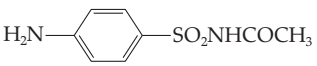
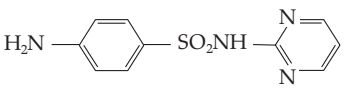
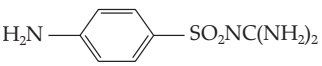
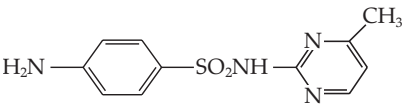
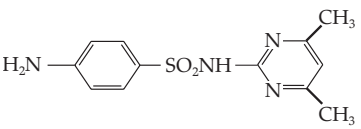
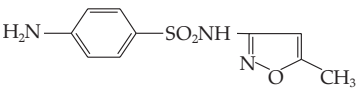
Apparatus

A CHEMITO Model 2100 UV-VIS Spectrophotometer (Chemito Technologies Pvt Ltd., India) with 1-cm matched cells was used for all spectral and absorbance measurements.

Reagents

All the reagents and solvents were of analytical grade. The drugs selected for study were procured from Charak Pharma Pvt. Ltd. (India), and their structures are given in Table I: sulfacetamide (SFA, 99.0%, Sigma Spain), sulfamethazine (SFMt, 99.0%, Sigma China), sulfadiazine (SFD, 99.0%, Sigma China) sulfaguanidine (SFG, 99.0%, Sigma Switzerland), sulfamerazine (SFMr, 99.0%, Sigma Belgium), sulfamethoxazole (SFMx, 99.0%, Sigma Belgium).

Table I. Sulfonamide drugs studied

Drug (code)	Structure
Sulfacetamide (SFA)	
Sulfadiazine (SFD)	
Sulfaguanidine (SFG)	
Sulfamerazine (SFMr)	
Sulfamethazine (SFMt)	
Sulfamethoxazole (SFMx)	

Standard solution of sulfonamide (1000 μg mL^{-1}) was prepared by dissolving 100 mg each sulfonamide in 2.0 mL of sulfuric acid (10 mol L^{-1}), then diluting with water to mark in a 100-mL volumetric flask. A working standard solution of each sulfonamide containing 25 μg mL^{-1} was prepared by further dilution and was standardized by the British Pharmacopoeia method (4) and the reported method (21). An 8-HQ solution (0.5%, *m/V*), sodium nitrite (1.0%, *m/V*) sulphamic acid (2%, *m/V*), sodium hydroxide (5 mol L^{-1}) and sulphuric acid (10 mol L^{-1}) were prepared in water.

General procedure

Aliquots of standard sulfonamide solutions (SFMx, SFD, SFA, SFMt, SFMr and SFG) were transferred into 25-mL calibrated flasks followed by 1.0 mL sulphuric acid to each. After cooling in an ice bath, 1.5 mL of sodium nitrite (1.0% *m/V*) was added under swirling. The solutions were allowed to stand for 5 min and then 2.5 mL of sulphamic acid (2.0%, *m/V*) was added, swirled and allowed to stand for 5 min. Then 2.0 mL of 8-HQ (0.5%, *m/V*) was added, along with 2.0 mL of sodium hydroxide (5 mol L^{-1}). The solution was made up to the mark with ethanol (95%), mixed thoroughly and after 5 min the absorbance was measured at 500 nm against a reagent blank, and the calibration graph was constructed.

The limit of detection (*LOD*) and quantification (*LOQ*) were calculated according to the current ICH guidelines (23) as 3.3 and 10 standard deviation of the blank (n = 6) respectively, divided by the slope of the calculation curve.

The range of the error was calculated using the following mathematical relation (24):

$$\frac{\pm t\,\mathrm{SD}}{\sqrt{\mathrm{n}}}$$

where t = 2.571 (95% confidence limit), n = number of replicate determinations.

Assay of commercial samples

Tablets. – The following tablet formulations were purchased from local commercial sources and used for the analysis: Septran tablet (Burroughs Wellcome, India) each containing 400 mg of SFMx, Sulphadiazine tablet (Rhone Poulenc, India) each containing 500 mg of SFD.

Twenty tablets were powdered and mixed thoroughly. An amount equivalent to 50 mg sulfonamide was then dissolved in 20 mL of sulphuric acid (1 mol L^{-1}) and filtered. The filtrate was made up to 100 mL and appropriate aliquots of the solution were treated as mentioned above in the general procedure.

Eye drops. – The following eye drop formulations were purchased from local sources and used for the analysis: Albucid (Nicholos-Pharmal India Ltd., India) containing 10 mg SFA mL^{-1}, Locula (East India Ltd., India) containing 10 mg SFA mL^{-1}.

A volume of 5 mL of eye drops (equivalent to 50 mg of SFA) was diluted with 2 mL of sulphuric acid (10 mol L^{-1}) and made up to 100 mL with water. The general procedure was then followed.

RESULTS AND DISCUSSION

Chemistry

Sulfa drugs could be readily diazotized in acidic medium and the diazonium cation would then react with a molecule of 8-HQ by electrophilic substitution at position-4 of the coupling agent. The proposed method involves diazotization of sulfonamide derivatives followed by their coupling with 8-HQ to produce a red coloured azo product. Job's method of continuous variation for determining the composition of the product indicated that the reactants and reagents reacted in the 1:1 ratio. The proposed mechanism of reaction between 8-HQ and the sulfonamide drug is illustrated in Fig. 1. To ascertain the absorption maxima for sulfonamide derivatives, specified amounts of sulfonamide derivatives were taken and the coloured reaction products were developed as mentioned in the general procedure, and the absorption maxima were found to be 500 nm. Fig. 2 shows the absorption spectrum of SFMx as the model compound. The resultant coloured product was found to be stable for about two days. The value of absorbance decreased above 30 °C. Hence, room temperature was preferred for the experiments. An attempt to increase the stability of the product beyond 48 hours failed.

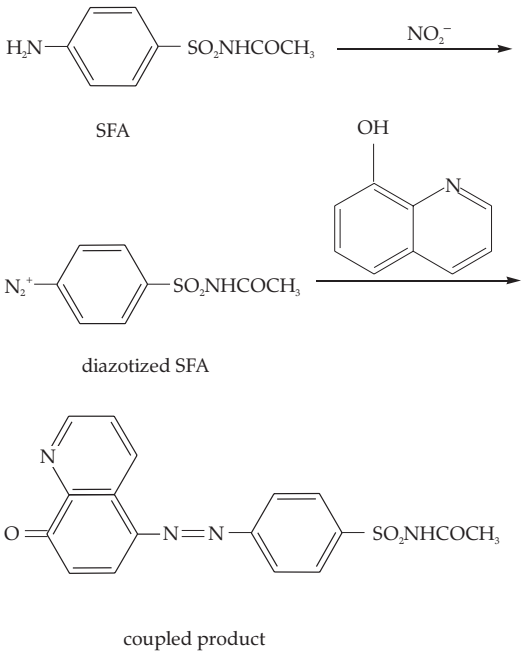


Fig 1. Scheme of the proposed reaction mechanism.

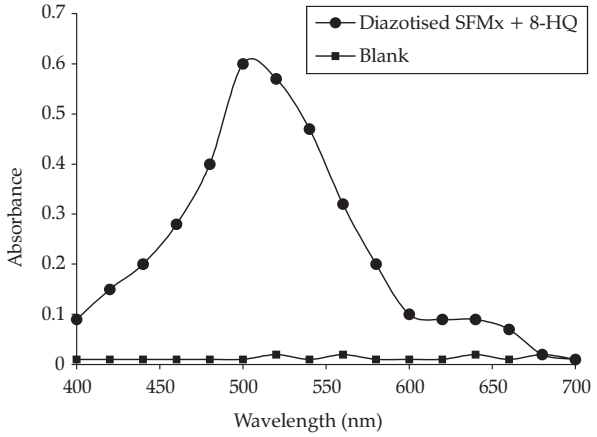


Fig. 2. Absorption spectrum of the reaction product of sulfamethoxazole (SFMx) with 8-HQ (λ_{max}= 500 nm).

Validation

The intraday precision of the proposed method was examined by carrying out six replicate determinations of sulfonamides (within Beer's law range) by the proposed method. Table II summarizes the RSD values (0.1–0.5%) and the range of error (0.20–0.35 at 95% confidence limit). The *LOD* was found to be in the range of 0.03 to 0.05 μg mL^{-1} and *LOQ* was in the range of 0.11 to 0.18 μg mL^{-1}. The recovery ranged from 97.3 ± 2.5% to 100.8 ± 1.2% (n = 6) (Table III).

The most promising feature of the proposed method is the freedom from interferences with the excipients commonly used in the pharmaceutical preparation of sulfonamide derivatives. Under optimum conditions, the effects of excipients and diluents such as talc, glucose, dextrose, lactose, *etc.*, were investigated. An amount far in excess of that used in the pharmaceutical preparation was added in half the limit of Beer's law and no effect due to these excipients was found under the proposed experimental conditions. The recovery range was from 99.2 ± 0.2% to 100.8 ± 0.4% (n = 6). The results are presented in Table IV.

Application of the proposed method

The applicability of the proposed method for the assay of different pharmaceutical formulations containing SFMx, SFD and SFA was examined for tablet and eye drops and the results were statistically compared with those obtained by the official method based on electrochemical titration (4) with $NaNO_2$ and the reported spectrophotometric method (21) based on the reaction of drug with acetylacetone-formaldehyde reagent. The *t*-test and *F*-test were carried out, which showed that the proposed method and other established methods are of comparable accuracy and precision. The results are summarized in Table V.

Table II. Some analytical parametres for the spectrophotometric determination of sulfonamide derivatives

Parameter	SFMx	SFD	SFA	SFMt	SFMr	SFG
Colour	Red	Red	Red	Red	Red	Red
λ_{max} (nm)	500	500	500	500	500	500
Stability (h)	48	48	42	48	46	48
Beer's law range (μg mL^{-1})	0.2–6.0	0.1–5.0	0.2–6.0	0.3–7.0	0.1–4.0	0.19–6.0
Limit of detection (μg mL^{-1})	0.04	0.05	0.04	0.04	0.03	0.03
Limit of quantitation (μg mL^{-1})	0.15	0.16	0.15	0.18	0.12	0.11
Molar absorptivity (L mol^{-1} cm^{-1})	3.38 x 10^4	3.7 x 10^4	2.81 x 10^4	3.48 x 10^4	3.8 x 10^4	3.7 x 10^4
Regression equation (y)[a]						
Slope (a)	0.143	0.145	0.124	0.130	0.136	0.125
Intercept (b)	0.011	0.005	0.007	0.004	0.003	0.012
Correlation coefficient (*R*)	0.9960	0.9984	0.9994	0.9980	0.9990	0.9992
RSD (%)	0.2	0.1	0.3	0.5	0.2	0.3
Range of error (95% confidencee level) (%)	0.3	0.2	0.4	0.3	0.2	0.3

[a] y = a γ + b where γ is the concentration in μg mL^{-1}.

Table III. Intraday accuracy and precision of the proposed method for SFMx

Nominal concentration SFMx (μg mL^{-1})	SFMx found (%)[a]		(e_r) (%)	Paired *t*-test
	Reported method (21)	Proposed method[b]		
1.0	99.7 ± 1.8	97.3 ± 2.5 *t* = 2.41 *F* = 1.93	2.4	2.005
2.0	99.2 ± 0.9	99.6 ± 1.3 *t* = 0.75 *F* = 2.10	0.4	
3.0	99.5 ± 1.2	99.7 ± 1.4 *t* = 0.35 *F* = 1.36	0.2	
5.0	97.3 ± 1.2	97.9 ± 1.0 *t* = 1.70 *F* = 1.44	0.7	
6.0	99.7 ± 1.0	100.8 ± 1.2 *t* = 2.12 *F* = 1.44	1.0	

[a] Mean ± SD, *n* = 6.
[b] Tabular *t*-value for d.f. 5 is 2.571; Tabular *F*-value for d.f. 5 is 5.05.

Table IV. Interference studies of commonly used excipients

Exicipient	Conc. (mg mL^{-1})	Recovery (%)[a,b]					
		SFMx	SFD	SFA	SFMt	SFMr	SFG
Gum acacia	5.0	99.5 ± 0.3	99.2 ± 0.3	100.5 ± 0.2	99.2 ± 0.3	100.1 ± 0.3	99.2 ± 0.3
Talc	5.0	100.1 ± 0.3	99.5 ± 0.3	99.2 ± 0.4	100.4 ± 0.3	100.1 ± 0.3	99.5 ± 0.3
Starch	5.0	99.2 ± 0.3	99.2 ± 0.3	99.2 ± 0.3	99.4 ± 0.2	100.2 ± 0.2	99.6 ± 0.3
Dextrose	3.5	99.2 ± 0.3	99.5 ± 0.3	99.6 ± 0.3	99.5 ± 0.3	99.6 ± 0.3	99.2 ± 0.3
Glucose	3.0	99.6 ± 0.3	99.5 ± 0.3	99.7 ± 0.2	99.2 ± 0.3	99.6 ± 0.3	95.5 ± 0.3
Lactose	4.0	100.2 ± 0.3	100.1 ± 0.3	100.2 ± 0.2	99.2 ± 0.5	100.7 ± 0.3	99.9 ± 0.2
Carboxymethyl-cellulose	4.0	100.5 ± 0.3	99.2 ± 0.2	100.2 ± 0.2	100.8 ± 0.4	100.6 ± 0.3	99.8 ± 0.4
Magnesium stearate	3.0	99.2 ± 0.3	99.2 ± 0.3	99.8 ± 0.2	99.7 ± 0.3	100.2 ± 0.2	99.9 ± 0.2
Sodium alginate	4.0	99.3 ± 0.6	99.6 ± 0.3	99.8 ± 0.3	99.2 ± 0.5	99.9 ± 0.2	99.1 ± 0.3
Vitamin B_6	3.8	100.3 ± 0.3	100.2 ± 0.3	100.6 ± 0.3	100.7 ± 0.4	100.3 ± 0.3	100.2 ± 0.3

[a] Concentration of sulfonamide drug: 4 μg mL^{-1}.
[b] Mean ± SD, n = 6.

The reported methods and the proposed method are compared in Table VI. For example, the proposed method is more simple and sensitive than the method including drug diazotization coupling with dopamine followed by complexation with molybdate ion reported earlier (28).

Table V. Determination of sulfonamide derivatives in pharmaceutical preparations

Sample	Label claim	Amount of drug found (in mg)[a]				
		Proposed method	BP method (4)	Reported method (21)	t-value	F-value
Septran (mg SFMx)	400	398.00 ± 0.70	397.00 ± 0.60	397.00 ± 0.80	2.29	1.44
Sulphadiazine (mg SFD)	500	497.00 ± 0.50	496.00 ± 0.60	496.00 ± 0.80	2.29	1.44
Albucid (mg mL^{-1} SFA)	10	9.90 ± 0.30	9.90 ± 0.30	9.75 ± 0.30	2.48	2.25
Locula (mg mL^{-1} SFA)	10	9.85 ± 0.20	9.80 ± 0.30	9.78 ± 0.30	2.50	1.96

[a] Mean ± SD, n = 6.
Theoretical t-value = 2.776; theoretical F-value = 6.39.

Table VI. Comparison of reported spectrophotometric methods with the proposed method

Reagent(s) used	Sulfonamide analyzed	λ_{max} (nm)	Beer's law limits ($\mu g\ mL^{-1}$)	Molar absorptivity ($L\ mol^{-1}\ cm^{-1}$)	Reference	Remark
p-Benzoquinone	SFMx and SFD	500	10–50		25	heating is needed
o-Chloranil	SFA	525	10–70		26	
Phenol and sodium hypochlorite	SFG	450	Not reported	1.65×10^4	27	
Dopamine	SFMx	500	0.1–7.0	2.67×10^4	28	diazotisation coupling, product is complexaton with molybdate
8-Hydroxy-quinoline (8-HQ)	SFMx	500	0.2–6.0	3.38×10^4	this paper	diazotization of drug followed by coupling with 8-HQ

The proposed method was found to be simple, rapid, selective and more sensitive than most of the spectrophotometric methods available in literature. It does not involve heating, extraction and consumes less time. The products are stable for a sufficient interval of time making the method useful in practice.

CONCLUSIONS

The proposed method is simple, sensitive and free from drastic experimental conditions such as heating. It is also accurate and precise enough to be successfully adopted as an alternative to the existing spectrophotometric method and evaluation of drugs in pharmaceutical preparations to assure a high standard of quality control.

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S A Ž E T A K

Osjetljiva spektrofotometrijska metoda za određivanje sulfonamida u farmaceutskim pripravcima

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U radu je opisana nova, jednostavna i osjetljiva spektrofotometrijska metoda za određivanje sulfonamida. Metoda se temelji na prevođenju sulfacetamida, sulfadiazina, sulfagvanidina, sulfamerazina, sulfometazina i sulfametoksazola u diazoderivate koji kondenzacijom s 8-hidroksikinolinom u alkalnom mediju daju crveno obojene produkte s maksimumom apsorpcije pri 500 nm. Beerov zakon vrijedi u koncentracijskom rasponu 0,1–7,0 μg mL^{-1}. Granice kvantifikacije i granice detekcije su 0,11–0,18, odnosno 0,03–0,5 μg mL^{-1}. Za predloženu metodu procijenjena je intermedijarska preciznost (RSD 0,1–0,5%) i točnost (analitički povrat 97,3–100,8). Uobičanjene pomoćne tvari u tabletama ne interferiraju tijekom određivanja. Metoda je uspješno primijenjena za analizu sulfonamida u farmaceutskim pripravcima.

Ključne riječi: sulfonamidi, diazotacija, 8-hidroksikinolin, spektrofotometrija, farmaceutski pripravak

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