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Two charge-transfer complex spectrophotometric methods for the determination of sulpiride in pharmaceutical formulations

Research Article

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Abstract: Two simple, rapid, accurate and sensitive spectrophotometric methods are described for the determination of sulpiride. They are based on charge transfer complexation between the drug as n-electron donor and p-chloranilic acid as π acceptor or iodine as σ-acceptor. These give highly coloured complexes with absorption maxima at 518 and 363, 294 nm, respectively. Beer's law linear ranges were 13.7 - 341.4 and 1.7 - 20.5 μg mL^{-1} for the p-chloranilic acid and iodine methods. The methods were successfully applied to the determination of the drug in Dogmatil® Fort tablets and the results compared with the official method. The complex association constants and standard free energy changes were calculated using Benesi-Hildebrand plots.

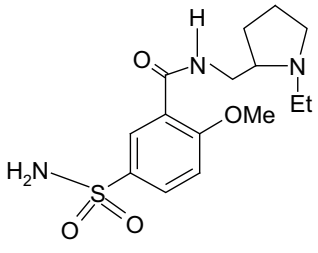
Keywords: *Spectrophotometric determination • Sulpiride • p-chloranilic acid • Iodine • Charge-transfer complexes*

1 Introduction

Sulpiride(SU),N-(1-ethylpyrrolidin-2-ylmethyl)-2-methoxy-5-sulfamoyl benzamide [15676-16-1], (see Scheme 1) is a substituted benzamide antipsychotic reported to be a selective antagonist of central dopamine (D_2, D_3 and D_4) receptors. It is used in the treatment of psychoses such as schizophrenia, and is also given in anxiety disorders, vertigo and benign peptic ulceration [1].

Several analytical methods have been used for SU determination including high performance liquid chromatography (HPLC) [2-12], thin layer chromatography (TLC) [13], capillary electrophoresis [14,15], flow injection, chemiluminescence [16], oscillopolarography [17], voltammetry [18], UV spectrophotometry [19-21], and fluorometry [22,23]. Two charge transfer spectrophotometric methods have been reported. The first [24] is based on heating the drug with tetracyanoquinodimethane in acetone at 60°C for 1 hour and measuring the absorbance at 575 nm after cooling. In the second method [25] the absorbance of the complex formed by reaction of the drug with chloranil for 100 seconds at 100°C in dioxane was measured at 590 nm.

The present work describes the use of p-chloroanilic acid (p-CA) or iodine for the spectrophotometric determination of SU in pure and dosage forms. In addition the composition, association constant and standard free energy changes (ΔG) of the charge transfer complexes formed between the drug and these reagents were determined.



Scheme 1. Structure of sulpiride.

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2. Experimental

2.1. Apparatus

A Shimadzu 1601 double beam UV-Vis spectrophotometer (2000H 50 W halogen lamp, deuterium lamp socket type) with a fixed slit width (2 nm), 500 nm min^{-1} scanning speed, wavelength range 190-1100 nm, connected to an IBM compatible computer and HP 600 inkjet printer was used with 1 cm matched quartz cells. The bundled software was UV PC Personal Spectroscopy version 3.91 (Shimadzu).

2.2. Materials and reagents

SU and Dogmatil® Fort tablets containing 200 mg SU per tablet were kindly supplied by Memphis Co. for Pharm. and Chem. Ind., Cairo, Egypt. All solvents were analytical grade.

Standard SU stock solution (5×10^{-3}M), was prepared by dissolving 170.7 mg of SU in a minimum amount of methanol and diluting to 100 mL with acetonitrile. Chloranilic acid (BDH Chemicals, Poole, UK) was freshly prepared (5×10^{-3} M) in acetonitrile. Resublimed iodine, (Riedel-De-Haen AG, Germany), 2×10^{-3} M solution in dichloroethane was freshly prepared.

2.3. Spectrophotometric procedures

2.3.1. p-chloroanilic acid method

Different amounts of SU was added to a 10 mL volumetric flask to give 13.7-341.4 µg mL^{-1}, 2 mL 5×10^{-3} Mp-CA was added, and the flask was filled to the mark with acetonitrile. The absorbance was measured at 518 nm against a reagent blank.

2.3.2. Iodine method

Different amounts of SU was added to a 10 mL volumetric flask to give 1.7-20.5 µg mL^{-1} SU, 2 mL 2×10^{-3} M iodine was added, and the flask was filled to the mark with acetonitrile. The absorbance was measured at 363 or 294 nm against a reagent blank.

2.4. Procedure for Dogmatil® Fort tablets

Twenty tablets were accurately weighed and powdered in a mortar. The required amount of powder was dissolved in the minimum amount of methanol, filtered into a 50 mL volumetric flask, the residue washed with methanol and completed to the mark with acetonitrile. The same procedure as for bulk samples was followed.

2.5. Stoichiometric relationship

Job's method of continuous variations [26] was employed to establish the reaction stoichiometry.

2.6. Association constant and free energy change

From 5×10^{-2} M SU solution (4 mL or 0.4 mL) was diluted to 10 mL with acetonitrile to give the highest concentration (2×10^{-2} or 2×10^{-3} M) for the p-CA and iodine methods respectively. Serial dilutions were prepared by diluting 7 mL of solution to 10 mL with acetonitrile until the lowest concentration was reached (4.8×10^{-3} or 4.8×10^{-4} M for the p-CA or iodine method, respectively). To 0.5 mL of each SU solution, 9.5 ml (5×10^{-2} M p-CA or 5×10^{-3} M iodine) was added and they were mixed well. The absorbance was measured at 518 nm (p-CA) or 363 nm (iodine) against a reagent blank.

3. Results and discussion

3.1. Spectral characterstics

p-CA is a π-acceptor forming charge transfer complexes with many n-donors [27]. p-CA in acetonitrile gave an absorption maximum at 430 nm while SU showed negligible absorption from 300-700 nm. On addition of SU to p-CA, the p-CA absorption showed a bathochromic shift with λ_{max} at 518 nm, forming a red-yellow complex (Fig. 1a). This was attributed to charge transfer complex formation between SU as an n-donor and p-CA as π-acceptor. The predominant p-CA chromogen is the radical anion probably formed by dissociation of an original donor-acceptor (DA) complex with SU.

$$\underset{\text{DA complex}}{D^{\bullet\bullet} + A \rightarrow [D^{\bullet\bullet} - A]} \xrightarrow{\text{Polar solvent}} \underset{\text{radical ions}}{D^{\bullet+} + A^{\bullet-}} \quad (1)$$

Dissociation of the complex is promoted by the high ionizing power of the solvent acetonitrile [28].

Highly intense charge transfer bands are common to complexes of n-donors with iodine [27]. Iodine in acetonitrile solution displayed an absorption peak near 467 nm while SU in acetonitrile gave a peak < 235 nm. On addition of SU to iodine in acetonitrile an orange-yellow complex formed. The iodine absorbance shifted to a shorter wavelength (hypsochromic shift) exhibiting two absorption maxima at 363 and 294 nm (Fig. 1b). The charge transfer complexation between the n-donor SU and the σ-acceptor iodine is followed by formation of a radical ion [29,30].

$$D + I_2 \rightarrow D - I_2 \quad (2)$$

$$D - I_2 \rightarrow (DI)^{+} I^{-} \quad (3)$$

$$(DI)^{+} I^{-} + I_2 \rightarrow (D - I)^{+} + I_3^{-} \quad (4)$$

As described by Mulliken [31], charge transfer transitions excite a donor electron to an empty orbital on the acceptor (from donor HOMO to acceptor LUMO).

The effect of different solvents, *i.e.,* acetonitrile, ethanol, methanol, dichloroethane, dichloromethane,

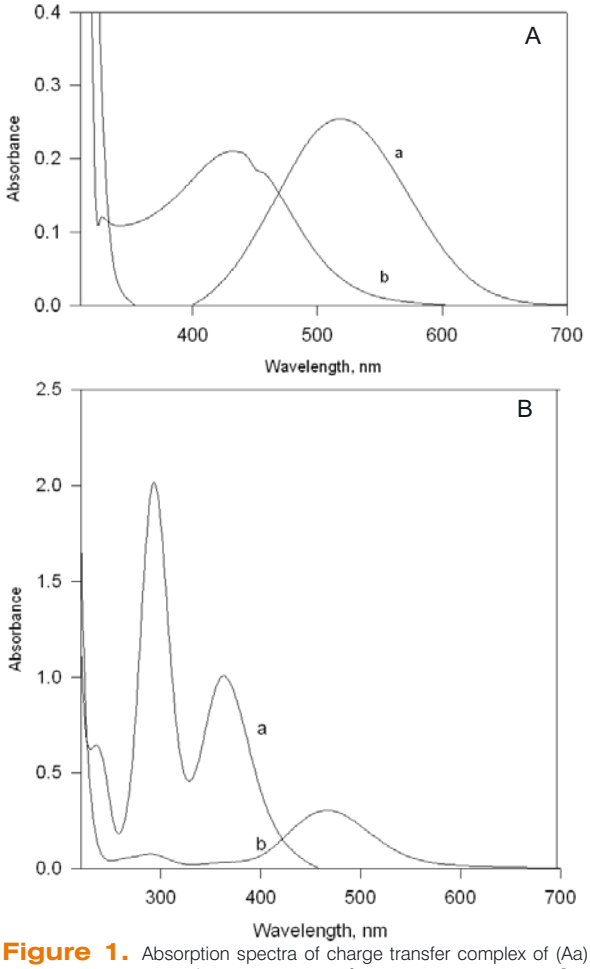

Figure 1. Absorption spectra of charge transfer complex of (Aa) 2×10^{-4} M SU with 1×10^{-3} M p-CA and (Ba) 4×10^{-5} M SU with 4×10^{-4} M iodine in acetonitrile, and (Ab and Bb) reagent blank against acetonitrile

chloroform, acetone and benzene were examined. Representative results for the p-CA method are shown in Fig. 2. Acetonitrile afforded maximum sensitivity. Its high dielectric constant promotes dissociation of the original charge-transfer complexes to radical ions. For other solvents the colour intensity was less (in acetone the colour disappears). The p-CA complex formed in water has low absorbance, and water is immisible with dichloroethane, the solvent for iodine.

When various amounts of p-CA (1-4 ml 5×10^{-3} M) or iodine (1-4 mL 2×10^{-3} M) were added to the 10 mL flasks containing fixed concentrations of SU (2×10^{-4} M for p-CA or 4×10^{-5} M for iodine), 2 mL of p-CA or 2 mL of iodine produced maximum and reproducible colour intensity. Higher reagent concentrations did not affect the colour intensity.

The optimum reaction time was determined by following the colour development at ambient temperature (25±5°C) of 2×10^{-4} M SU plus 1×10^{-3} M p-CA or 4×10^{-5} M SU plus 4×10^{-4} M iodine, respectively. Complete colour development was instantaneous for both reactions and the colour remained stable for more than 24 hours (p-CA) or 6 hours (iodine).

Job's method of continuous variation [26] revealed a 1:1 ratio for the drug and each reagent, as shown in Fig. 3.

3.2. Association constant and standard free energy change

The association constant for the complexation of SU with either p-CA or iodine was calculated using the Benesi-Hildebrand equation [32]:

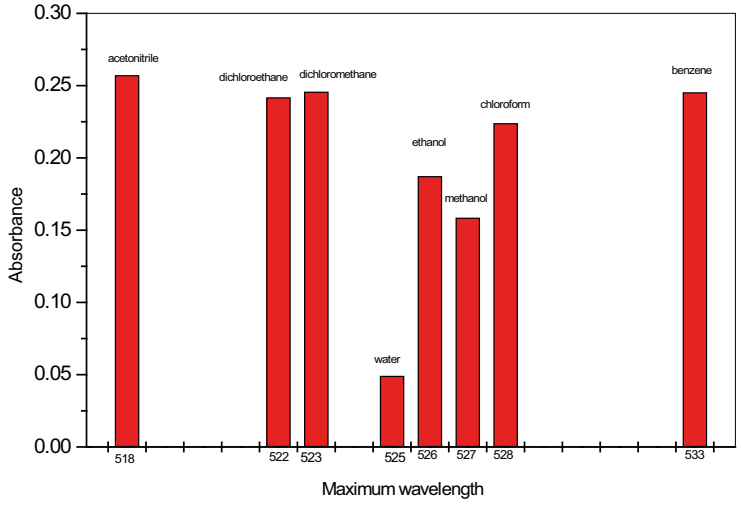

Figure 2. Effect of different solvents on charge transfer complex of 2×10^{-4} M SU with 1×10^{-3} M p-CA.

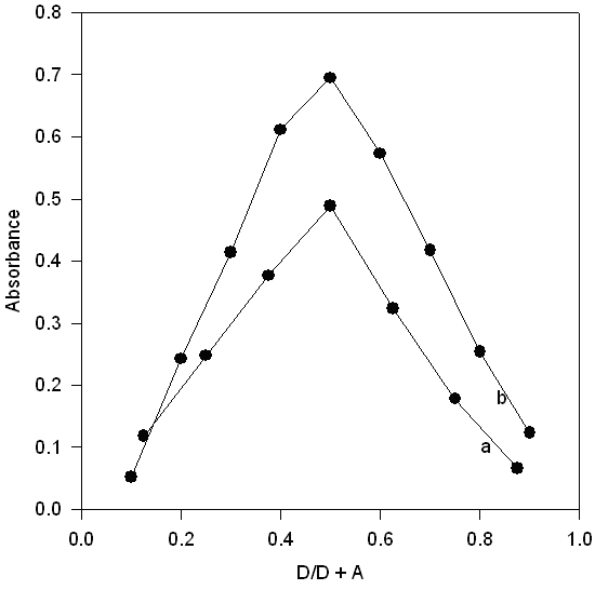

Figure 3. Job's method for SU complexes. Total molar concentration = 8×10^{-4} and 1×10^{-4} M for p-CA and iodine, respectively; (a) p-CA, λ = 518 nm and (b) Iodine, λ = 363 nm.

Table 1. Association constant K_C^{AD}, molar absorptivity values ε^{AD}, correlation coefficients r from Benesi-Hildebrandt plots for the complex and the calculated ΔG^0.

Parameter	p-CA	Iodine
K_C^{AD}	0.28×10^2	0.93×10^3
ε^{AD}	9.43×10^2	6.4×10^3
r	0.9999	0.9995
ΔG^0 (kJ mol^{-1})	-8.26	-16.94

Table 2. Spectral data for the reaction of sulpiride with p-chloranilic acid and iodine.

Parameters	Chloranilic acid	Iodine	
λ_{max}	518	363	294
Regression equation			
Slope	0.0037	0.0815	0.1536
Intercept	-0.0057	-0.0386	-0.0571
Correlation coefficient (r)	0.9998	0.9997	0.9981
Beer's law linear range, μg mL^{-1}	13.7 – 341.4	1.7-20.5	1.7-20.5
Ringbom linear range, μg mL^{-1}	68.3 - 273.1	6.8-13.7	6.8-13.7
Detection limit, μg mL^{-1}	3.41	0.32	0.37
Quantification limit, μg mL^{-1}	11.37	1.07	1.23
Molar absorptivity, ε L mol^{-1} cm^{-1}	1.25×10^3	2.70×10^4	5.17×10^4
Sandell sensitivity, S ng cm^{-2}	0.273	0.013	0.066

$$\frac{A_0}{A^{AD}} = \frac{1}{\varepsilon^{AD}} + \frac{1}{K_C^{AD}\varepsilon^{AD}} x \frac{1}{D_0} \quad (5)$$

Where A_0 and D_0 are the total concentrations of the acceptor and donor respectively, A^{AD} is the absorbance of the complex, ε^{AD} is the molar absorptivity of the complex and K_C^{AD} the complex association constant (L mol^{-1}). On plotting the values A_0/A^{AD} *vs.* $1/D_0$, straight lines were obtained (Fig. 4), from which the association constant and correlation coefficient were determined (Table 1). The standard free energy change (ΔG^0) for the complexation is given by [33]

$$\Delta G^0 = -2.303\ RT \log K_C \quad (6)$$

where R is the gas constant (8.314 J mol^{-1} K) and T the Kelvin temperature.

3.3. Quantitation

Calibration curves for SU with p-CA or iodine were constructed by plotting absorbances *vs.* concentrations. The intercepts, slopes, and correlation coefficients were calculated using the method of least squares (Table 2). Beer's law is obeyed over concentration ranges of 13.7 - 341.4 (p-CA) or 1.7 - 20.5 μg mL^{-1} (iodine). The mean molar absorptivity (ε), Sandell sensitivity (S) and Ringbom optimum range were also determined (Table 2).

The limits of detection (LOD = 3s/k) and limit of quantitation (LOQ = 10s/k) were calculated [34], where s is the standard deviation of replicate determinations in the absence of analyte under the same conditions as sample analysis and k is the slope. The LOD were 3.41 and (0.32, 0.37) μg mL^{-1} and LOQ were 11.37 and (1.07, 1.23) μg mL^{-1} for the p-CA and iodine methods.

The intra-day and inter-day (day-to-day) precision expressed as relative standard deviation were 0.53 and 1.61% (n = 8) for 2×10^{-4} M SU using the p-CA method or 1.47 and 1.53% (n = 8) for 2×10^{-5} M SU using the iodine method.

The robustness [35] was also examined by evaluating the effect of small changes in acceptor concentration and λ_{max}. None of the changes significantly affects drug recovery (Table 3); this provides an indication of the methods' reliability.

The effect of excipients was also studied. No interferences (<2% change) were observed in the presence of a 100-fold excess of talc, starch, glucose, maltose or magnesium stearate.

3.4. Pharmaceutical preparation analysis

The methods were applied to the determination of SU in Dogmatil® Fort tablets (200 mg SU). Drug recovery

Table 3. Influence of small variations of operational conditions on the mean recovery of 2×10^{-4} M SU (p-CA) and 2×10^{-5} M SU (iodine), (n = 3).

Variable	% Recovery	SD
p-CA method		
λ_{max}		
514	99.6	0.418
516	99.9	0.431
518	100.1	0.442
520	100.1	0.437
522	100.0	0.418
Acceptor (5×10^{-3} M)		
1.5 mL	100.8	0.083
2.0 mL	100.2	0.616
2.5 mL	100.3	0.645
Iodine method		
λ_{max}		
361	99.0	0.817
363	99.5	0.811
365	99.1	0.807
Acceptor (2×10^{-3} M)		
1.5 mL	99.0	0.580
2.0 mL	98.8	0.871
2.5 mL	98.9	0.822

Table 4. Determination of SU in Dogmatil® Fort tablets by the proposed methods.

	Added mg	Recovery, %	SD	RSD, %
Chloranilic acid method	47.81	98.86	1.428	1.444
	68.3	96.06	0.991	1.032
	136.6	96.07	0.706	0.735
Iodine method	0.034	97.17	2.094	2.155
	0.068	97.88	2.356	2.407
	0.103	96.01	2.572	2.679

Table 5. Statistical comparison between results of Dogmatil® Fort tablets by the proposed and official methods.

Parameter	Chloranilic acid method	Iodine method	Official method [36]
Mean recovery, %	97.00	97.02	97.57
SD	1.042	2.341	1.00
RSD	1.074	2.413	1.025
F-ratio (9.28)[a]	1.086	5.480	
t-test (2.447)[b]	0.790	0.432	

Average of four determinations for the proposed and official methods.
a: Tabulated F-value at 95% confidence level.
b: Tabulated t-value at 95% confidence level and 6 degrees of freedom.

was satisfactory (Table 4) and the results were in good agreement with label claims and with values obtained using the official British Pharmacopoeia method [36] (Table 5)

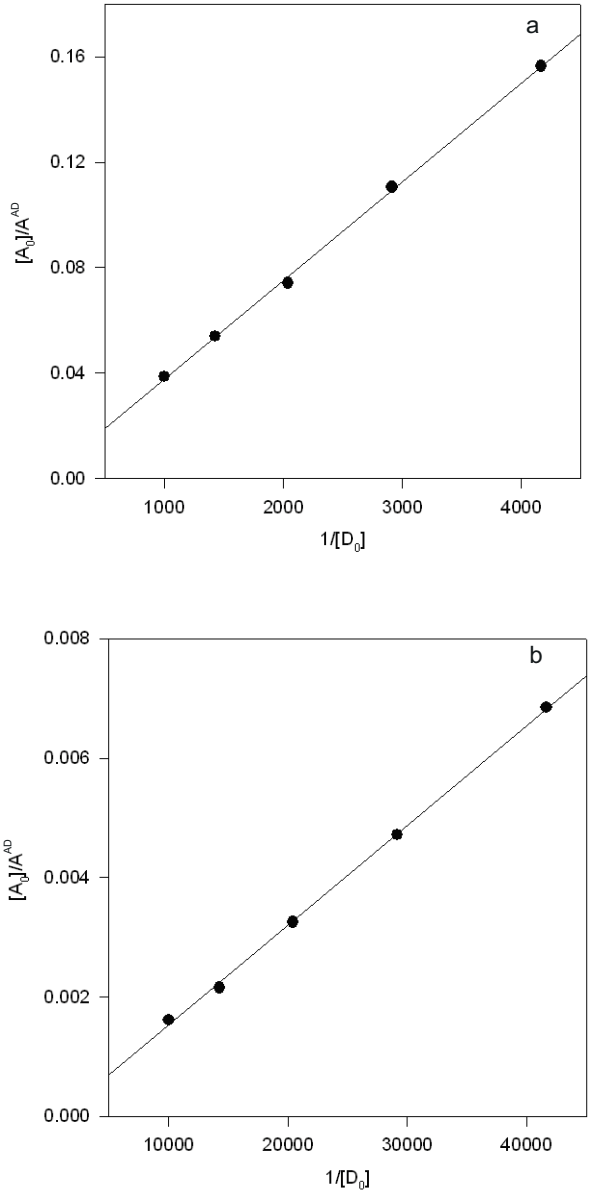

Figure 4. Benesi-Hildebrand plot for a) SU-chloranilic acid complex, λ = 518 nm and b) SU–iodine complex, λ = 363 nm.

Statistical comparison of the accuracy and precision of the proposed methods with the official method (Table 5) was performed using Student's t- and the F-ratio tests at a 95% confidence level [37]. The t- and F-values did not exceed the theoretical values; there is no significant difference in accuracy or precision between the proposed and the official method.

4. Conclusion

The charge transfer complexations between sulpiride as electron donor and p-chloranilic acid as π acceptor or iodine as σ-acceptor were studied spectrophotometrically in acetonitrile. The coloured complexes were used in simple, rapid, and accurate spectrophotometric methods suitable for routine analysis of the drug in quality control laboratories. The iodine method is more sensitive than the p-chloranilic acid method due to the higher molar absorptivity. The proposed methods are simpler, more sensitive, and less time consuming than the published charge transfer methods (complete colour development was instantaneous and heat is not needed) [24,25].

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