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Spectrophotometric Determinations of Pimozide and Mefloquine Hydrochloride through Ion Association Complex Formation

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Three simple spectrophotometric methods (Method A, Method B and Method C) have been developed for the determination of pimozide (PZ) and mefloquine hydrochlonde (MQ) in bulk and pharmaceutical formulations. These methods are based on the formation of ion association complex involving tertiary nitrogen of PZ or secondary nitrogen of MQ and dye [wool fast blue BF (WFB BF, λ_{max} 580 nm, method A); naphthol blue black (NBB, λ_{max} 580 nm, method B); supracen violet 3B (SV 3B, λ_{max} 560 nm, method C]. Beer's law limits, precision and accuracy of these methods are checked by the UV reference method. The results obtained are reproducible and are statistically validated and so found to be suitable for the assay of PZ or MQ in bulk and pharmaceutical formulations.

Key Words: Spectrophotometric, Determination, Pimozide, Mefloquine hydrochloride, Ion association complex.

Pimozide[1] (PZ) [2H-benzimidazol-2-one, 1-[1-[4,4-bis(4-fluorophenyl)-butyl-4-piperidinyl]-1,3-dihydro-] is an antipsychotic agent while mefloquine hydrochloride[1] (MQ) [4-quinoline methanol-α-(2R)-2-piperidinyl-2,8-bis-(trifluoro- methyl)-monochloride] is an antimalarial. PZ is official in BP[2] and USP[3] while MQ is official in BP[2]. The reference method chosen for the assay of PZ or MQ in bulk and dosage forms is UV method[3,4]. Literature survey revealed that only few methods are reported which include HPLC (PZ[5], MQ[6]), TLC (PZ[7], MQ[8]), GC-MS (PZ[9], MQ[10]), titrimetric (PZ[11,12]), fluorometric (PZ[13], MQ[14]), UV (PZ[3], MQ[4]) and visible spectrophotometric methods (PZ[15], MQ[16,17]). This paper describes three visible spectrophotometric methods for the determination of PZ or MQ based on the formation of an ion association complex with acid dye namely wool fast blue BF (WFB BF), naphthol blue black (NBB) or supracen violet 3B (SV 3B) which is extractable into chloroform. The protonated aliphatic tertiary or secondary nitrogen (positive charge) of PZ or MQ in acid medium is expected to attract the oppositely charged portion of the dye (—SO_3^-) and behaves as a single unit being held together by electrostatic attraction in method A, method B or method C. These methods have been extended to pharmaceutical formulations containing PZ or MQ.

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A Milton Roy Spectronic 1201 and Systronics 106 digital spectrophotometer with 1cm matched quartz cells were used for spectral and absorbance measurements in the UV and visible regions respectively. An Elico LI-120 digital pH-meter was used for pH measurements.

All the reagents and chemicals used were of analytical grade. Aqueous solutions of WFB BL (Fluka, 3.26×10^{-3} M), NBB (Chroma, 3.2×10^{-3}M), SV-3B (Chroma, 4.63×10^{-3} M) and glycine-HCl buffer solution (pH 1.5) were prepared by dissolving the required amounts in triple distilled water. The commercially available tablets were procured from local market.

Standard and sample solutions

Stock solutions (1 mg/mL) of PZ or MQ were prepared separately by dissolving 100 mg of PZ or MQ (bulk or tablet powder equivalent) initially in 10 mL of 0.1 M HCl followed by dilution to 100 mL with distilled water. Working solutions of PZ or MQ were prepared by stepwise dilution of each stock solution with distilled water to get suitable concentrations of PZ (20 μg/mL, 100 μg/mL, 100 μg/mL) or MQ (20 μg/mL, 100 μg/mL, 100 μg/mL) for methods A, B and C respectively.

Assay procedure

Aliquots of the standard PZ (10–50 μg for method A, 50–250 μg for method B or 40–200 μg for method C) or MQ (8–40 μg for method A, 20–100 μg for method B or 20–120 μg for method C) were placed in a series of 125 mL separating funnels. Exactly 6.0 mL of pH 1.5 buffer solution and 2.0 mL of dye (WFB BL, method A; NBB, method B; SV 3B, method C) solution were added and the total volume of aqueous phase was adjusted to 15 mL with distilled water. To each separating funnel 10.0 mL of chloroform was added and the contents were shaken for 2 min. The two phases were allowed to separate and the absorbance of the separated chloroform layer was measured at 580 nm (method A or method B) or 560 nm (method C) against similar reagent blank during the stability period (immediate 60 min). The amount of PZ or MQ present was computed from the appropriate calibration graph.

The optimum conditions for the colour development of the methods were established by varying parameters [effect of pH (1.0–3.0), nature of dye and its concentrations (phenazine {wool fast blue BL, C.I., No. 50315; azocarmine G, C.I. No. 50085; lissamine blue BF, C.I. No. 50230}, azo-{naphthol blue 12 BR; tropaeolin 00, C.I. No. 13080; tropaeolin 000, C.I. No. 14600; naphthol blue black, C.I. No. 20470} amino anthraquinone (supracene violet 3B, C.I. No. 60730; alizarine Red S, C.I. No. 58005}), ratio of aqueous to organic phase, shaking time] one at a time keeping others fixed and observing the effect produced on the absorbance of coloured species. The best ones (WFB BL, NBB, SV 3B) were used in the present investigations. The stoichiometric ratio of PZ or MQ to the dye was found as 1 : 1 with WFB BL, 2 : 1 with NBB and 1 : 1 with SV-3B through slope analysis method.

The optical characteristics such as Beer's law limits, molar absorptivity and Sandell's sensitivity for these methods are given in Table-1. The precision of each method was found by measuring absorbances of six replicate samples containing

TABLE 1
OPTICAL CHARACTERISTICS AND PRECISION

Parameters	PZ			MQ		
	Method A	Method B	Method C	Method A	Method B	Method C
λ_{max} (nm)	580	580	560	580	580	560
Beer's law limits (μg mL^{-1})	0.5–6.0	1–15	2–20	0.3–2.0	0.8–12	0.8–12
Sandell's sensitivity (μg cm^{-2}/0.001 absorbance unit)	0.010	0.0207	0.0367	0.0065	0.0173	0.02
Molar extinction coefficient coefficient (L mol^{-1} cm^{-1})	4.596×10^4	2.249×10^4	1.257×10^4	6.636×10^4	2.405×10^4	2.074×10^4
Relative standard deviation (%)*	0.305	0.306	0.396	0.125	0.443	0.408
% Range of error (confidence limits)						
0.05 level	0.320	0.322	0.416	0.132	0.472	0.429
0.01 level	0.502	0.537	0.651	0.206	0.739	0.673
Correlation coefficient (r)	0.9999	0.9999	0.9999	0.9999	0.9999	0.9999
Regression equation†						
Slope (b)	9.97×10^{-2}	4.80×10^{-2}	2.71×10^{-2}	1.527×10^{-1}	5.89×10^{-2}	4.97×10^{-2}
Intercept (a)	-1.733×10^{-3}	-4.955×10^{-4}	1.5×10^{-3}	8.0×10^{-4}	-1.333×10^{-4}	2.226×10^{-3}

*Six replicate samples.
†y = a + bc where c is concentration.

TABLE 2: ANALYSIS OF PHARMACEUTICAL FORMULATIONS BY PROPOSED AND REFERENCE METHODS

Drug/Pharmaceutical formulations*	Labelled amount (mg)	Amount found (mg) by proposed methods†			Reference methods PZ^3, MQ^4	% Recovery hy proposed method‡		
		Method A	Method B	Method C		Method A	Method B	Method C
PZ Tablets-I	2	1.96 ± 0.017 F = 1.52 t = 1.84	1.99 ± 0.011 F = 3.6 t = 0.1	1.98 ± 0.021 F = 1 t = 1.54	2.00 ± 0.071	98.76 ± 0.70	99.85 ± 0.63	99.93 ± 1.05
Tablets-II	2	1.99 ± 0.02 F = 4 t = 0.82	1.99 ± 0.01 F = 1 t = 1.37	1.999 ± 0.021 F = 4.7 t = 1.99	2.01 ± 0.010	100.05 ± 0.82	99.76 ± 0.63	99.68 ± 1.06
Tablets-III	2	1.98 ± 0.028 F = 1.25 t = 0.09	1.07 ± 0.015 F = 2.7 t = 0.68	1.97 ± 0.036 F = 2.07 t = 2	1.99 ± 0.025	99.91 ± 0.78	99.01 ± 0.64	98.98 ± 1.74
Tablets-IV	10	9.97 ± 0.115 F = 1.18 t = 0.19	9.85 ± 0.15 F = 1.56 t = 1.1	9.97 ± 0.14 F = 1.25 t = 0.047	9.96 ± 0.125	99.76 ± 0.08	99.56 ± 0.59	99.78 ± 1.43
MQ Tablets-I	250	249.77 ± 0.398 F = 4.99 t = 2.0	251.31 ± 0.74 F = 1.44 t = 0.37	251.05 ± 0.96 F = 1.16 t = 1.94	250.97 ± 0.89	99.90 ± 0.16	100.57 ± 0.30	100.31 ± 0.38
Tablets-II	250	249.88 ± 0.86 F = 1.7 t = 1.72	250.59 ± 0.54 F = 1.49 t = 0.46	251.05 ± 0.96 F = 2.12 t = 1.08	250.38 ± 0.66	99.95 ± 0.34	100.23 ± 0.21	100.41 ± 0.38
Tablets-III	250	249.14 ± 1.06 F = 1.11 t = 1.39	250.35 ± 1.64 F = 2.66 t = 0.19	251.21 ± 1.05 F = 0.92 t = 1.15	250.38 ± 1.01	99.65 ± 0.42	100.26 ± 0.49	100.28 ± 0.25
Tablets-IV	250	249.54 ± 1.42 F = 2.54 t = 1.76	250.36 ± 0.62 F = 2.06 t = 0.97	251.05 ± 0.96 F = 1.16 t = 0.15	250.17 ± 0.89	99.81 ± 0.56	100.14 ± 0.24	100.44 ± 0.38

*Four types of tablets (PZ or MQ) from four different pharmaceutical companies.

†Average standard deviation of six determinations; the t- and F-test values refer to comparison of the proposed methods with the reference method,. Theoretical values at 95% confidence limits, t = 2.57, F = 5.05.

‡Recovery of 10 mg added to the pharmaceutical formulations (average of three determinations).

known amounts of drug and the results obtained are incorporated in Table-1. Regression analysis using the method of least squares was made to evaluate the slope(b) intercept (a) and correlation coefficient (r) for each system (Table-1). The relative standard deviation and % range of error at 95% confidence level are also given in Table-1. The accuracy of the methods was ascertained by comparing the results by proposed and reference methods (UV) statistically[18] by t- and F-test (Table-2). This comparison shows that there is no significant difference between the results of studied methods and those of reference ones. The similarity of the results is an obvious evidence that during the application of these methods, the excipients that are usually present in pharmaceutical formulations do not interfere in the assay of proposed methods.

The higher λ_{max} values of all the proposed methods have a decisive advantage since the interference from the associated ingredients should be generally less at higher wavelengths than at lower wavelengths. Thus the proposed visible spectrophotometric methods are simple and sensitive with reasonable precision and accuracy and constitute better alternatives to the existing ones to the routine determination of PZ or MQ in bulk and unit dosage forms.

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