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Development of Stability indicating spectrophotometric method for determination and validation of "Risperidone" in formulation and bulk drug

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Abstract

Simple, accurate, economical and reproducible Visible-spectrophotometric methods have been developed for estimation of Risperidone in both bulk and tablet formulation. The developed methods are validated according to ICH guidelines.To develop new methods O -phenonthrolin, ARS, WFBBL, PNA are used as reagents. All the methods are obeyed Beer's law. These four methods can be utilize as quality tools for quantification of Risperidone in pure and formulations.

Keywords: Visible-spectrophotometric methods, O –phenonthrolin method, ARS method, WFBBL method, PNA method

Introduction:

Risperidone is a potent antipsychotic drug which is mainly used to treat schizophrenia (including adolescent schizophrenia), schizoaffective disorder, the mixed and manic states associated with bipolar disorder, and irritability in people with autism.[1-3] Risperidone belongs to the class of atypical antipsychotics. It is a dopamine antagonist possessing antiserotonergic, antiadrenergic and antihistaminergicproperties.

Side effects of Risperidone might include significant weight gain and metabolic problems such as diabetes mellitus, as well as tardive dyskinesia and neuroleptic malignant syndrome. Risperidone and other antipsychotics also increase the risk of death in patients with dementia.[4-6]

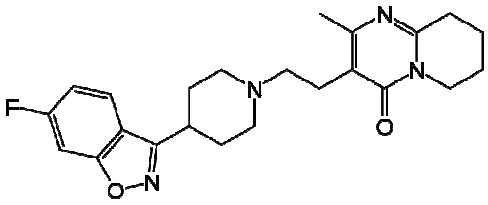

Figure.1. Structure of Respiridone

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Applications and Side effects of Respiridone

Risperidone is used for the treatment of schizophrenia, bipolar disorder and behavior problems in people with autism. Antipsychotic medications such as Risperidone have a slight benefit in people with dementia, they have been linked to higher incidences of death and stroke. Akathisia**,** Anxiety**,** Sedation**,** Dysphoria**,** Insomnia**,** Low blood pressure, Muscle stiffness**,** Muscle pain**,** Tremors**,** Hypersalivation **,** Constipation **,** Nasal congestion, Rash.

Materials and Methods

Instrumentation:

Double beam UV visible spectrophotometer UV 2301 and standard Quartz cuvetts with lid of 10mm path length was used.

Preparation of working standard drug solution:

The standard Respiridone (100 mg) was weighed accurately and transferred to volumetric flask (100 ml). It was dissolved properly and diluted up to the mark with methanol to obtain final concentration of 1000 µg /ml (stock solution I). 20 ml of stock solution I was diluted to 100 ml with methanol (Stock solution II, 200µg/ml) and the resulting solution was used as working standard solution.

Preparation of reagents:

o-phenonthrolin : Weighed accurately 200 mg of o-phenonthrolin and was dissolved in 100 ml of distilled water with warming.

Fe (III) solution: Accurately 250 mg of anhydrous ferric chloride was weighed and was taken in a 100 ml graduated volumetric flask. It was dissolved in little amount of distilled water and the final volume was made up to the mark with distilled water.

Alizarin Red S (ARS) solution: weighed 200 mg of ARS and is dissolved in 100ml of distilled water.
Woll Faster Blue Black (WFBBL) solution: weighed 200 mg of WFBBL and is dissolved in 100ml of distilled water.
P-Nitro Aniline (PNA) solution: Accurately 100 mg of PNA was weighed and was taken in a 100 ml graduated volumetric flask. It was dissolved in 0.2 M HCl solution and made up to the mark.

$NaNO_2$ solution: accurately 100 mg of $NaNO_2$ was weighed and was taken in a 100 ml graduated volumetric flask. It was dissolved in distilled water and made up to the mark.

NaOH solution (4 %, 1M): Accurately 4g of NaOH was weighed and was taken in a 100ml graduated volumetric flask. It is dissolved in distilled water and made up to the mark.

P^H 2 Buffer solution: the solution was prepared by mixing 306ml of 0.1M tris sodium citrate with 694ml of 0.1M HCL and the P^H adjusted to 2.

HCl solution (1N): Prepared by diluting 86 ml of conc. HCl to 1000 ml with distilled water and standardized.

Procedures of Developed Spectro photometric methods

The following new procedures were developed on the basis of reactions of the functional groups present in Respiridone. Systemic and detailed studies of the various parameters involved were described under results and discussion in this chapter for the determination of Respiridone in bulk, dosage and pharmaceutical formulations.

O-phenonthrolin Method :(M1)

From the standard stock solution II of Respiridone, appropriate concentration(30 to180 ppm) is pipetted out in to a 10 ml volumetric flasks add 0.5 ml $FeCl_3$ solution and 2 ml of 1,10 Phenonthroline were added. The tube was heated in water bath up to 30 min. after cooling the tube 2 ml of acid was added and make up to 50 ml with distilled water. Make up to 50 ml volume. The absorbance of the formed color was measured after 5min at 500 nm against a reagent blank.

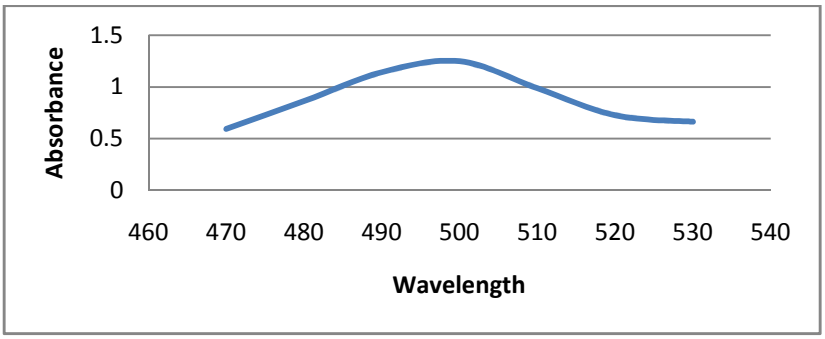

Figure 2: Absorption spectrum of Respiridone with O-phenonthrolin

ARS Method: (M2)

In a series of 125 ml separating funnels containing aliquots of standard drug (15-90ppm) solution was taken. To this 6ml of HCl solution and 2ml of ARS solutions were added successively. The total volume of the aqous phase in each separating funnel was adjusted to 15ml with distilled water. To each separating funnel 10ml 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 440nm against a similar reagent blank.

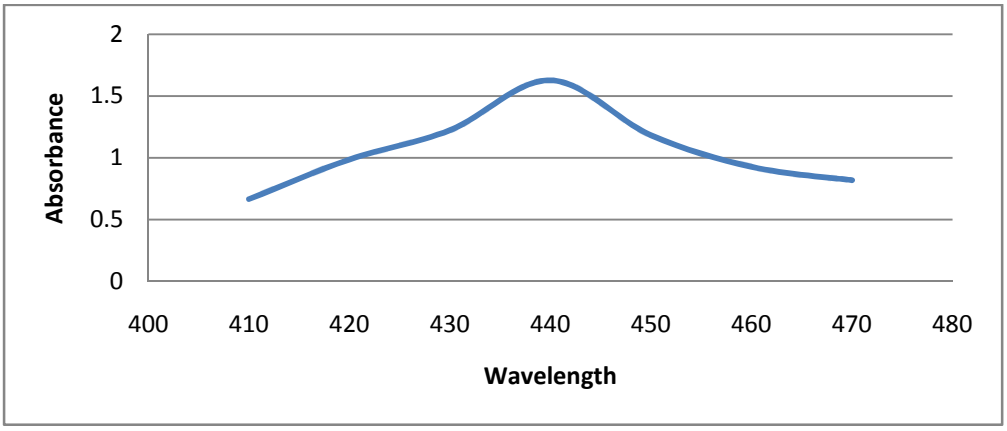

Figure.3: Absorption spectrum of Respiridone with Alizarin Red S

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WFBBL Method: (M3)

In a series of 125 ml separating funnels containing aliquots of standard drug solution (5-30ppm) was taken. To this 6ml of HCl solution and 2ml of WFBBL solutions were added successively. The total volume of the aqous phase in each separating funnel was adjusted to 15ml with distilled water. To each separating funnel 10ml 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 600nm against a similar reagent blank.

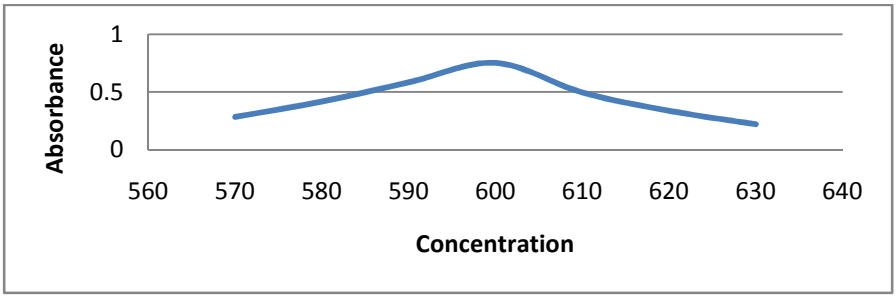

Figure.4: Absorption spectrum of Respiridone with Woll Faster Blue Black

PNA method: (M4)

In a 10 ml graduated test tubes 1.0 ml of PNA solution and 1.0 ml of NaNO2 solution were successively added and allowed to stand for 2 min. Later, standard drug of elected concentration (20-120ppm) is delivered into the test tube. Then 1.5 ml of NaOH solution was added and the volume in each tube was made up to 10 ml distilled water. Solution attains green color. The maximum absorbance was measured at 440nm against a reagent blank (colorless).

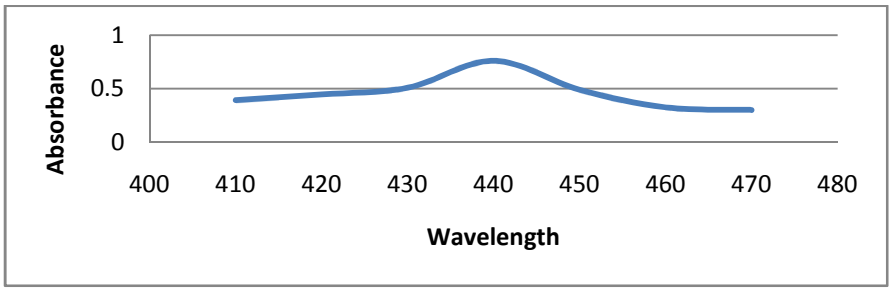

Figure.5: Absorption spectrum of Respiridone with PNA

Results and Discussion

Spectral Characteristics:

In order to ascertain the optimum wavelength the absorption spectra were scanned in the wavelength region of 380-760nm against a corresponding blank. The results were graphically presented in the figures: 2,3,4,5 respectively.

For each method optical characteristics such as absorption maxima, Beer`s law limit, molar absorptivity is determined and were present in Table.1. The precision were found by analyzing six replicate samples containing known amount of drug and results are summarized in Table.2

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The linearity ranges of Respiridone are found to be 20-80ppm, 10-60 ppm, 30-90ppm, 2-8ppm, for M1 to M4 respectively. A linear correlation was found between absorbance and concentration of Respiridone. The graphs showed negligible intercept and are described by the equation: Y = a + bX (where Y = absorbance of 1-cm layer of solution; a = intercept; b = slope and X = concentration in ug mL-1 max) .Regression analysis of the Beer's law data using the method of least squares was made to evaluate the slope (b), intercept (a) and correlation coefficient(r) for each system according to ICH guide.

The accuracy of the proposed methods was further ascertained by performing accuracy studies. The relative standard deviations of results for the proposed were very low and the values are within the range below 2. It indicates that the high accuracy and precision for the proposed methods. The recovery results were very close to the actual range and it revealed that co-formulated substances did not interfere in the determination.

S.NO	Parameter	M1	M2	M3	M4
1	Wavelength Max	500nm	440nm	600nm	440nm
2	Concentration Range	20-80ppm	10-60ppm	30-90ppm	2-8ppm
4	Correlation coefficient	0.9994	0.9992	0.9993	0.9992
5	Slope	0.012983	0.010507	0.12052	0.071184
6	Intercept	0.015952	0.001357	0.018836	-0.00728
7	RSD of Precision	0.289	0.638	0.279	0.459
8	Average recovery	99.05	99.5	99.84	100.5
9	Stability period	220 min	180 min	360min	240 min
10	LOD	0.2 ppm	0.5 ppm	0.05 ppm	0.01 ppm
11	LOQ	0.4ppm	1.0 ppm	0.1ppm	1ppm
12	% Assay of Formulation	99.2	99.56	99.47	99.63

Table.1: Optical and regression characteristics, Precision and Accuracy of the proposed method for Respiridone

SNO	M1	M2	M3	M4
Concentration	40 ppm	30 ppm	50 ppm	4 ppm
1	0.563	0.324	0.628	0.273
2	0.562	0.323	0.624	0.274
3	0.565	0.321	0.625	0.276
4	0.564	0.321	0.628	0.275
5	0.561	0.326	0.627	0.276
6	0.565	0.325	0.628	0.276
% of RSD	0.289	0.638	0.279	0.459

Table.2: Precision of the proposed methods

Method	Recovery	Concentration in ppm	Amount found in ppm	% of recovery
M1	100%	40	39.62	99.05
M2	100%	30	29.85	99.5
M3	100%	50	49.92	99.84
M4	100%	4	4.02	100.5

Table.3: Recovery of the proposed methods

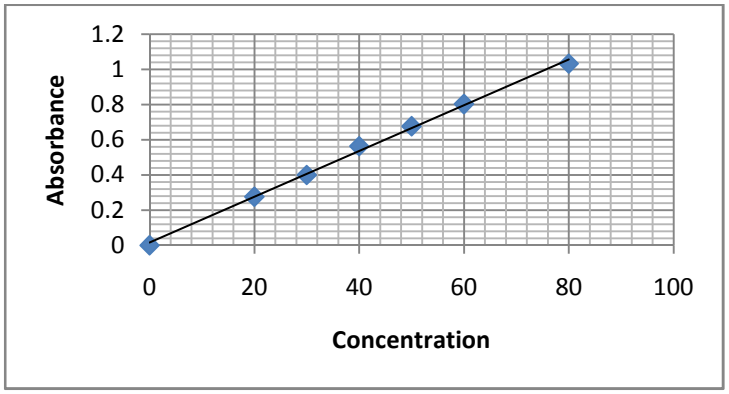

Figure.6: Beer`s law plot of Respiridone with ARS Method

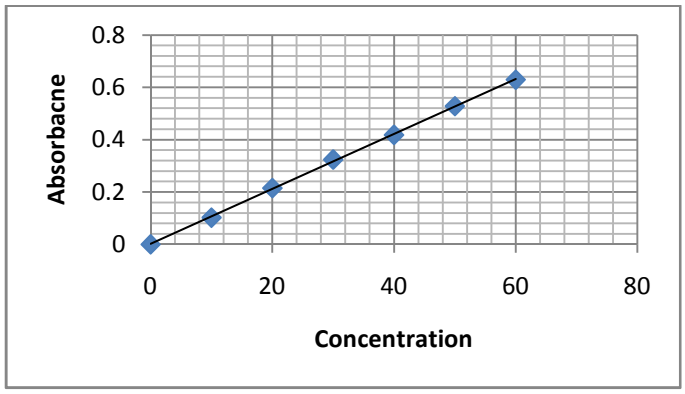

Figure.7: Beer`s law plot of Respiridone with PNA Method

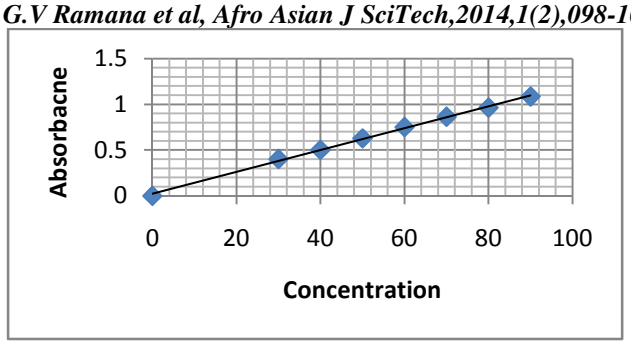

Figure.8: Beer`s law plot of Respiridone with WFBBL Method

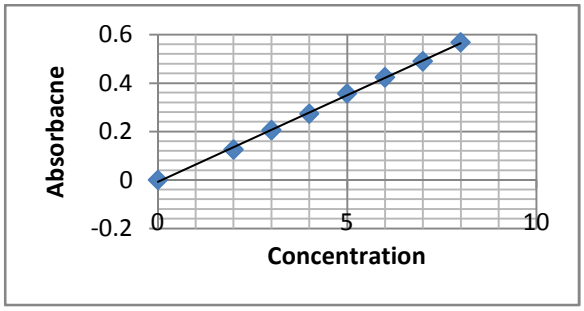

Figure.9: Beer`s law plot of Respiridone with 1,10 phenonthrolin

5.1.2 Application of spectro photometric method: Respiridone Quantification in Commercial Formulations:

In order to check the validity of the proposed methods, Respiridone was determined in commercial formulation. From the results of the determination it is clear that there is close agreement between the results obtained by the proposed methods and the label claim. These results indicating that there was no significant difference between the proposed methods and the reference methods in respect to accuracy and precision.

S.NO	Method	Formulation	Amount prepared	Amount found	% Assay
1	M1	RISPERDAL 0.5 mg	40 ppm	39.86	99.65
2	M2	RISPERDAL 0.5 mg	30 ppm	29.95	99.83
3	M3	RISPERDAL 0.5 mg	50 ppm	49.63	99.26
4	M4	RISPERDAL 0.5 mg	4ppm	3.99	99.75

Table.4: Assay of the proposed methods

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5.1.3 Nature of colored species:

Although structures of colored species have not been established experimentally, which is beyond the scope of the present investigation, they may be postulated by taking appropriate analogy.

Method M_1:

Method M1 is based on the mechanism of oxidation followed by complex formation, where in the initial reaction the anti-oxidant undergoes oxidation in the presence of ferric chloride and then the oxidized ferric chloride reacts with 1,10- phenanthroline and the drug to form a orange red colored complex which exhibits maximum absorption at wavelength of 500 nm.

Method M_2 and M_3:

In ARS and WFBBL methods drug being a base form an ion association complex with acid dyes ARS and WFBBL. The formed complex is extractable in to chloroform from the aqueous phase. The protonated nitrogen positive charge of the drug molecule in acid medium is expected to attack the positive charge of the dye. Hence form a colored complex which is extracted with chloroform. The obtained color chromogen shows absorbance at 440nm for ARS Method and 600nm for WFBBL method.

Method M_4:

PNA method involves the diazotization of PNA with sodium nitrate fallowed by coupling with drug in alkaline medium. The formed PNA- DRUG complex develop green color, the developed color can be estimated by using spectrophotometer at a wavelength 440 nm.

The proposed method was validated as per ICH guidelines. The parameters studied for validation were specificity, linearity, precision, accuracy, robustness, and system suitability, limit of detection and limit of quantification.

Conclusion:

The proposed methods are found to be simple, precise, accurate, reproducible and sensitive and can be utilize as quality tools for quantification of Risperidone in pure and formulations.

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