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DEVELOPMENT AND VALIDATION OF NEW SPECTROPHOTOMETRIC METHODS FOR THE QUANTITATIVE ESTIMATION OF SILODOSIN IN BULK DRUG AND PHARMACEUTICAL FORMULATIONS

Karazgi Kishwar Jahan[1]* and Malipatil SM[2]

[1]JJT University, Vidyanagri Churu-Bisau Rd. Jhunjhunu, Rajasthan, India.
[2]HKE'S College of Pharmacy, Gulbarga, India.

ABSTRACT

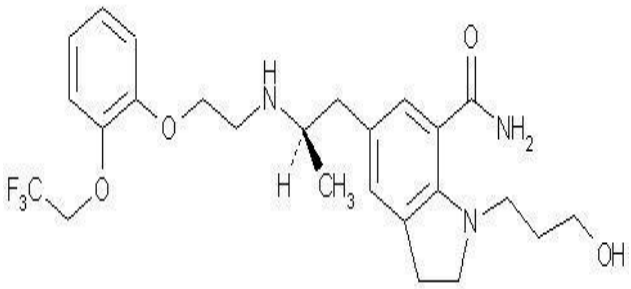
Three simple, sensitive, accurate and rapid spectrophotometric methods A, B and C have been developed for the quantitative estimation of Silodosin in bulk drug and also pharmaceutical formulations. Method A is a UV-spectrophotometric method in which Silodosin was dissolved in alcohol showing λmax 269nm.The method is linear in the concentration range of 10-50µg/ml. Methods B and C are based on oxidation followed by complex formation reaction. In method B and C Silodosin reacts with 1,10-phenanthroline and 2,2'-bipyridyl to form orange red colored chromogen which shows maximum absorbance at 507nm and 518nm for methods B and C respectively. Linearity range for method B was between 2-10µg/ml and that for method C was between 4-20µg/ml. Results of the analysis were validated statistically. All the validation parameters were within the acceptable range and prove the precision, sensitivity and applicability of the methods for the routine quantitative determination of Silodosin in its dosage form.

Keywords: Silodosin, 1,10-phenanthroline, 2,2'-bipyridyl, UV-Spectrophotometer.

INTRODUCTION

Silodosin [1] is a highly selective alpha 1A-adrenoreceptor antagonist approved for the treatment of the signs and symptoms of benign prostatic hyperplasia [2] (BPH). Its clinical pharmacology profile offers a number of advantages including uroselectivity, once daily (QD) dosing, a standard dose of 8 mg QD that does not need to be adjusted according to age and the feasibility of concomitant treatment with phosphodiasterase type 5 (PDE 5) inhibitors and antihypertensive agents. Relative to Tamsulosin, Silodosin has less cardiovascular side effects. Silodosin, a selective antagonist of alpha-1 adrenoreceptors, has chemical name 1-(3-Hydroxypropyl)-5-[(2R)-2-({2-[2-(2,2,2-trifluoroethoxy) phenoxy]ethyl} amino)propyl]-2,3-dihydro-1H-indole-7-carboxamide [3-4] and the molecular formula is $C_{25}H_{32}F_3N_3O_4$ with a molecular weight of 495.53. The structural formula of Silodosin is:

SILODOSIN



Literature survey reveals that number of analytical methods are available for estimation of Doxazosin [5-6], Tamsulosin [7-9], Gabapentine [10-12] and other BPH drugs but only one UV spectrophotemetric [13] method and one HPLC [14] method has been developed for the

Corresponding Author:- Karazgi Kishwar Jahan Email:- jahan_kish@rediffmail.com

quantitative estimation of Silodosin in formulation and one LC-MS/MS [15] method for the determination of Silodosin in human plasma. Silodosin is a key drug for the treatment of BPH with a number of advantages including uroselectivity, once daily dosing, standard dose of 8 mg QD that does not need to be adjusted according to age and the feasibility of concomitant treatment with phosphodiasterase type 5 (PDE 5) inhibitors and antihypertensive agents. Lack of analytical methods for the quantitative estimation drives us for the development of spectrophotometric methods for the routine analysis of Silodosin.

EXPERMENTAL WORK

Equipment

Electronic balance, UV-Visible Spectro photometer (Systronic 2203) with matched quartz cells.

Reagents

Reagents required such as alcohol, 1,10-phenanthroline, ferric chloride, 2,2'-bipyridyl are of analytical grade, purchased from different sources, capsule dosage form of Silodosin (Silodal 4mg and 8mg) was purchased from local market.

Preparation of standard stock solution

Standard stock solution was prepared by dissolving 100mg of Silodosin in about 40ml alcohol in a 100ml volumetric flask and volume was made upto the mark with alcohol (1000µg/ml)

Preparation of working stock solution

10ml of standard stock solution was taken in a 100ml volumetric flask and volume was made upto the mark with alcohol (100µg/ml).

Method A

10,20 and 30µg/ml solutions were prepared by diluting working stock solution with alcohol and scanned between 200 to 400 nm and 269nm was selected as λmax.

Five different aliquots were prepared by taking 1,2,3,4 and 5ml from working stock solution in different 10ml volumetric flask and final volume was made upto 10ml with alcohol. Calibration curve was plotted using absorbance values against concentration.

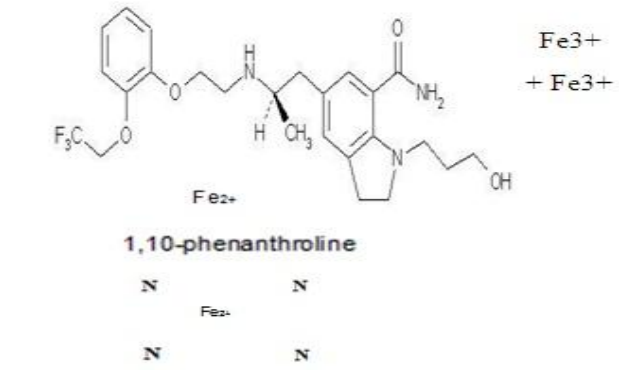
Method B

In this method five aliquots from 2 to 10 µg/ml were prepared by taking 0.2 to 1ml solution from working stock solution in different 10 ml volumetric flasks, to each of the flask 0.5ml of 0.5% ferric chloride was added followed by 1ml of 0.2% w/v of 1,10- phenanthroline. Aliquots were heated at 60°C for about 10 minutes to complete the reaction, allow to cool at room temperature and then volume was made upto the mark with alcohol. Absorbance of aliquots was measured at 507nm against reagent blank and calibration curve was prepared.

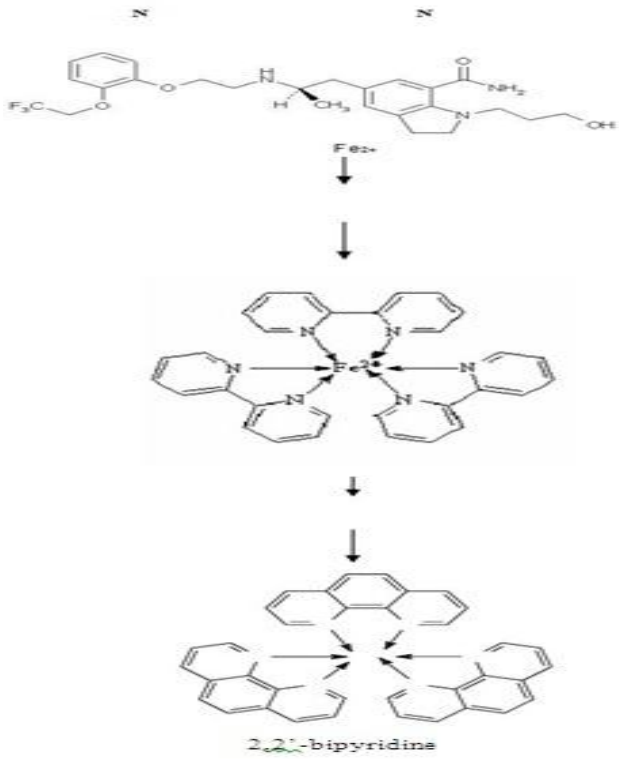
Method C

Aliquots of drug were prepared by pippetting 0.4, 0.8, 1.2, 1.6 and 2ml of working stock solution in different 10ml volumetric flasks. To each of the flask 0.5ml of 0.5% w/v ferric chloride and 1ml 0.02M 2,2'-bipyridyl were added respectively. The solutions were heated on water bath at 60°C for 10 minutes for complete development of color. Cool at room temperature and volume was made upto the mark with alcohol. Absorbance was measured against reagent blank prepared simultaneously selecting 518nm as λmax and calibration curve was prepared.

METHOD B



METHOD C



RESULTS AND DISCUSSION

Optical parameters

In order to ascertain the optimum wavelength of maximum absorption (λ max) of UV spectrophotometric method and of the colored species formed in each of the two visible spetrophotometric methods, specified amount of Silodosin was taken and the colors were developed following the above mentioned procedures individually. The absorption spectra were scanned on spectrophotometer in the wavelength region of 200-380nm for UV spectrophotometric method and 380-800 nm for colorimetric methods against corresponding reagent blanks. Appropriate λ max for the three methods was selected.

Optical Characteristics

The absorbance at appropriate wave lengths of a set of solutions containing different amounts of Silodosin and specified amount of reagents (as described in the recommended procedure) were noted against corresponding reagent blank.

The Beer's law plot of the system illustrated graphically. Least square regression analysis was carried out for the slope, intercept and correlation coefficient. Beer's law limits, molar absorptivity, Sandell's sensitivity for Silodosin with each of mentioned reagents was calculated table-1.

Parameters fixation

In developing these methods, a systematic study of the effects of various relevant parameters in the methods concerned were under taken by veriying one variable at a time (OVAT) and controlling all other parameter to get the maximum color development, reproducibility and reasonable period of stability of final colored species formed.

Linearity range

The linearity of analytical method is its ability to elicit test results that are directly proportional to the concentration of analyzed sample within a given range. The range of analytical method is the interval between the upper and lower levels of analyte that have been demonstrated within a suitable level of precision, accuracy and linearity. Linearity ranges of the three proposed methods were given in table no 1.

Method

The results obtained in colorimetric methods were based on oxidation followed by complex formation reaction of Silodosin with 1,10-phenanthroline and 2,2'-bipyridyl using ferric chloride to form an orange red colored chromogen that exhibited maximum absorption at 507nm and 518 nm respectively against the corresponding reagent blanks. The effect of various parameters such as concentration, volume of reagents, order of addition of reagents and solvent for final dilution were studied by means of control experiments varying one parameter at a time.

Precision

Precision of each one among the three proposed spectrophotometric methods were ascertained separately from the absorbance values obtained by actual determination of a fixed amount of Silodosin in final solution. The percent relative standard deviation and percent range of error (at 0.05 and 0.01 confidence limits) were calculated for the proposed methods and presented in table no 1.

Accuracy

Recovery studies were carried out at three different levels i.e., 50%, 100% and 150%, of label claim following standard addition method. Results were statistically calculated and found between the range of 100.04-100.56, 99.1-100.56 and 99.49-100.42 for methods A, B and C respectively. This shows high accuracy of the proposed methods (table 3).

Table 1. Optical characteristic and regression analysis data

Sr.No.	Optical Characteristic	Method A	Method B	Method C
1.	λmax.	269	507	518
2.	Linearity range	10-50	2-10	4-20
3.	Sandell's sensitivity μg/cm^2	0.03	0.009	0.012
4.	Molar absorptivity	4.2218 x 10^3	3.1119 x 10^4	2.3785 x 10^4
5.	Correlation coefficients(r)	0.99991	0.99996	0.9994
6.	Slope (b)	0.01585	0.06215	0.046925
7.	Intercept (a)	0.0133	0.0047	0.0327
8.	RSD of Precision	0.76438	1.146	0.464
9.	Average recovery	100.28±0.26	99.9± 0.75	100.02±0.478
10.	Color Stability period	----------	80min	75min
11.	LOD	0.779	0.237	0.0153
12.	LOQ	2.36066	0.71868	0.614
13.	Percentage assay of formulation	100.16±0.268	99.66±0.353	99.83±0.749

	(Mean±SD)			
14.	Range of error			
	0.05 confidence limit	1.64687×10^{-3}	3.9837×10^{-3}	2.6246×10^{-3}
	0.01 confidence limit	2.18687×10^{-3}	5.28999×10^{-3}	3.4853×10^{-3}
15.	Standard error of method	6.25×10^{-4}	1.51185×10^{-3}	9.9608×10^{-4}

Table 2. Analysis of Silodosin Capsule Formulation with Statistical Evaluation (n=6)* (METHOD A, B, C)

Method	Label Claim	Reference Method Mean	%Drug estimated Mean*± SD	%RSD	SEM*
A	4mg	98.2	99.97±0.20	0.201	0.082
	8mg	98.7	100.35±0.67	0.667	0.247
B	4mg	98.2	99.91±1.195	1.196	0.488
	8mg	98.7	99.41±0.98	0.986	0.400
C	4mg	98.2	99.30±0.95	0.962	0.387
	8mg	98.7	100.36±0.48	0.479	0.196

*Mean of 6 determinations

Table 3. Recovery Studies Using the Proposed Method With Statistical Evaluation (n=6)*(METHOD A, B, C)

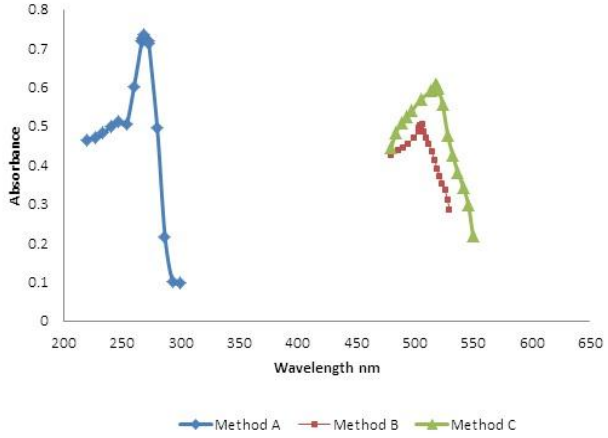
Method	Concentration of formulation	Label claim	Pure drug spiked	Statistical results			SEM*
				Mean*	SD	%RSD	
A	50%	8mg	4mg	100.04	0.136	0.136	0.055
	100%	8mg	8mg	100.56	0.55	0.547	0.224
	150%	8mg	12mg	100.26	0.568	0.567	0.231
B	50%	8mg	4mg	99.1	1.338	1.350	0.546
	100%	8mg	8mg	100.16	1.401	1.399	0.571
	150%	8mg	12mg	100.56	0.685	0.681	0.279
C	50%	8mg	4mg	100.15	0.88	0.878	0.359
	100%	8mg	8mg	99.49	0.811	0.812	0.331
	150%	8mg	12mg	100.42	0.682	0.679	0.278

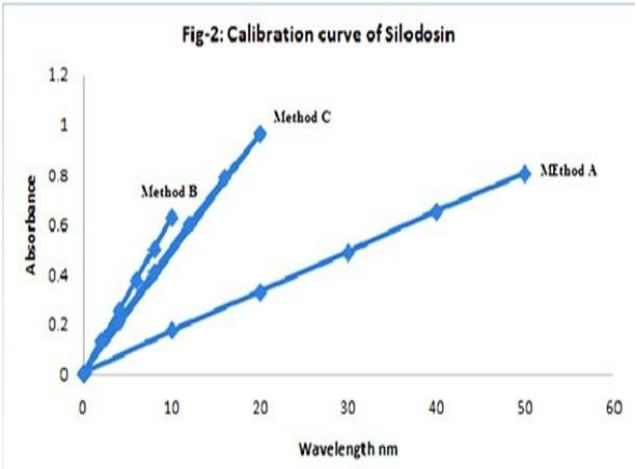
*Mean of 6 determinations

Table 4. Color stability studies (METHOD B, C).

Method B	**Concentration**	**6µg/ml**							
	Time(min)	10	20	30	40	50	60	70	80
	Absorbance	0.375	0.376	0.375	0.375	0.374	0.376	0.375	0.370
Method C	**Concentration**	**12 µg/ml**							
	Time(min)	10	20	30	40	50	60	65	70
	Absorbance	0.609	0.608	0.610	0.609	0.611	0.609	0.608	0.608

Fig 1. Absorbtion Spectrum of Silodosin





Color Stability

To study the stability of the developed color for proposed methods middle concentration of linearity range was selected. Color was developed by adding 0.5ml of 0.5% w/v $FeCl_3$ solution and 1ml of 0.2%w/v solution of 1,10-phenanthroline to drug. The resulting solution was heated at 60^oC for 10 min, allow to cool at room temperature and volume was made up to 10 ml with alcohol. Color stability was measured against time.

For method C, to the drug solution, 0.5ml of 0.5% w/v solution of $FeCl_3$ and 1ml of 0.02M 2,2'- Bipyridyl was added. The resulting solution was heated at 60^oC for 10 min, cooled at room temperature and volume was made upto 10 ml with alcohol. Colors for the two methods were found to be stable for sufficient period of time. Results for the color stability studies were provided in table no 4.

CONCLUSION

The proposed methods can be used for determination of Silodosin in bulk drug as well as in formulations. These methods are rapid, simple and have great sensitivity and accuracy. Developed methods make use of simple reagents, which an ordinary analytical laboratory can afford. Methods are sufficiently sensitive to permit determination even down to 10µg/ ml. Hence we can conclude that the proposed methods are suitable for routine determination of Silodosin in its formulation.

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