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TWO DIRECT SIMPLE VISIBLE SPECTROPHOTOMETRIC ASSAY METHODS OF SOLIFENACIN SUCCINATE IN ORAL TABLET FORMULATIONS

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ABSTRACT

Two direct, simple visible spectrophotometric methods (Method -I & II) were described for the assay of solifenacin succinate in pure and in oral dosage forms. The proposed methods (I&II) are based on the ion association complex reactions between the mentioned drug (solifenacin succinate) and the basic dyes (Methylene blue and Methylene Violet) respectively. Beer-Lambert plots showed good correlation in the concentration range of 2.0-10µg/mL for methods–I &II respectively. The proposed methods were applied to commercially available dosage forms (tablets) of solifenacin succinate and the results were statistically compared with the results obtained by the reported method[7] with recovery studies. The proposed methods offered the advantages of being simple and economical that can be applied without the need for expensive instrumentation and reagents in quality control analysis.

Keywords: Solifenacin succinate, Visible spectrophotometry, Method validation.

INTRODUCTION

Solifenacin succinate[1-3](Fig.-1), a competitive muscarinic acetylcholine receptor antagonist used for the treatment of overactive bladder with or without urinary incontinence. Being an antagonist, it prevents the binding of acetylcholine to M3 receptor subtype thereby reducing smooth muscle tone in the bladder, thereby allowing the bladder to retain larger volumes of urine and reducing the number of incontinence episodes.

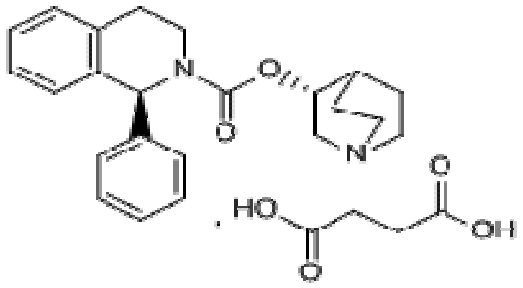

Fig.-1: Chemical Structure of Solifenacin succinate

Monograph for solifenacin succinate is available only in European Pharmacopoeia[4]. Chemically, Solifenacin succinate is butanedioic acid (3R)-1-azabicyclo [2.2.2] octane-3-yl(1S)-1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate with an empirical formula of $C_{27}H_{32}N_2O_6$ and molecular weight of 480.5528 gms/mol. It is freely soluble in water, Glacial acetic acid, dimethyl sulfoxide and methanol. Presently six brands of generics of solifenacin succinate are available in local pharmacy that is formulated for oral administration. In the current study for one commercial formulation of solifenacin succinate in the brand name of BISPEC (Dr.Reddy Laboratories Ltd;Dosage strengths -10mg) was used .

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Literature survey revealed only three spectrophotometric methods[5-7] were reported to the present date for the determination of solifenacin succinate in tablet dosage forms. As such no attention was made in developing new visible spectrophotometric methods by exploiting the analytically useful functional groups present in solifenacin succinate.In this direction, the author made an attempt to develop economically viable visible spectrophotometric assay methods for solifenacin succinate in its tablet formulations. Accordingly, the author developed two new, simple visible spectrophotometric methods for the assay of solifenacin succinate in tablet formulations.

EXPERIMENTAL

Material and Methods

In the present study UV - Visible digital spectrophotometer [Model SL-157,Elico] along with 1.0cm matched quartz cells were used for the spectral measurements. A Systronics digital pH meter [Model-361] was used for pH measurements.

Reagents Preparation

The reagents used in this assay are of analytical grade and the reagent solutions were prepared using double distilled water.

Method –I [Methylene Blue; MB (0.1% W/V)]

Prepared by dissolving, accurately weighed 100mg of Methylene Blue (MB) reagent in 100 ml of distilled water and subsequently washed with chloroform to remove chloroform soluble impurities.

Method - II [Methylene Violet; MV (0.1% W/V)]

Prepared by dissolving 100mg of Methylene Violet (MV) reagent in 100ml of distilled water and subsequently washed with chloroform to remove chloroform soluble impurities

Preparation of Standard Drug Solutions

A 1.0mg/ml solution was prepared by dissolving 100mg of pure solifenacin succinate (99%) in 100ml of methanol and this stock solution was diluted step wise with distilled water to get the working standard solutions of solifenacin succinate with concentrations of 40µg/ml for Methods-I and II respectively.

Assay of Oral Dosage Formulations

Accurately weighed a portion of finely ground oral tablet powder (BISPEC-10mg) equivalent to 100mg of solifenacin succinate was carefully transferred into a 100ml volumetric flask. Add 80ml of methanol to the same flask, and shaken well for 20 min. Later the contents were diluted up to the mark with methanol and filtered through Whatman filter paper No 41. This filtrate was evaporated to dryness to obtain drug residue and was finally dissolved as described in standard solution preparation. These solutions were analyzed as under recommended procedures described.

Recommended Procedure

After several experimental trials and studies of various parameters involved, the following procedures were recommended for the assay of solifenacin succinate in pure and in formulations.

Method-I

Aliquots of working standard drug solution (0.5-2.5ml,40µg/ml) were placed separately into a series of 125ml separating funnels and 1.0ml of pH 9.8 buffer solution was added. To above funnels 1.0ml of methylene blue (MB) solution was added and the total volume of aqueous phase was adjusted to 10ml with distilled water. To the above funnels 10ml of chloroform was added and the contents were mixed thoroughly with intermittent shaking for 2 min. Later, the organic colored layer (chloroform) was collected and the absorbance was measured at 615nm against reagent blank. The amount of drug present was obtained using Beer's Lambert plot. (Fig.-4).

Method-II

Aliquots of standard drug solution (0.5-2.5ml,40µg/ml) were placed separately into a series of 125ml separating funnels and 1.0ml of pH 9.8 buffer solution were added. To above funnels 1.0ml of methylene violet (MV) reagent solution was added and the total volume of aqueous phase was adjusted to 10ml with distilled water. Then 10ml of chloroform was added in each separating funnel and the contents were mixed by shaking for 2 mins respectively. The organic colored layer was collected and the absorbance was measured at 620nm against a reagent blank(Chloroform). The amount of drug present was deduced using Beer's Lambert plot. (Fig.-5).

RESULTS AND DISCUSSION

Optimization of experimental conditions

Preliminary experimental trials were carried out by the author in this accord in the developing procedures for the new methods (I and II) spectrophotometrically by observing and studying the effects produced on the absorbance of the colored species obtained by changing one parameter and keeping the other parameters fixed.

Method-I and II

The optimum conditions in these methods were made based on the study of the effects on absorbance values with the use of various parameters such as the type of acid for the buffer, conc. of dye MB (Method-I), or MV (Method-II), choice of organic solvent, shaking time and the stability of the colored species and the results are incorporated in Table-1.

Table -1: Optimum conditions established for methods-I & II for solifenacin succinate

Parameter used	Optimum Range	Conditions in Procedure	Observation
λ_{max} in nm for methods I & II	610-620nm 610-630nm	615nm 620nm	--
Effect of buffer on color development	9.0-10.0	pH-9.8	Variations of the pH<9.0 and >9.8 resulted in low absorbance values
Volume in ml of buffer needed for maximum color intensity	0.5-1.5	1.0mL	Optimum volume of 1.0ml of buffer was sufficient for maximum color development
Volume in ml of reagent solution MB (Method-I) MV(Method-II)	 0.1-1.0 0.1-1.0	1.0mL	1.0 ml of MB and MV were necessary to obtain broad range of beer's law limits
Choice of organic solvents for extraction of colored complex	Chloroform, Methanol	Chloroform	Chloroform was preferred as it forms colored drug-dye complex
Effect of shaking time (min)	1-5	2	Constant absorbance values were obtained for the shaking period of 2 min.
Stability of the colored species	-----	12hrs	----

Spectral Characteristics

After establishing optimized conditions in each developed methods (I and II) with specified amounts of solifenacin succinate was analyzed separately by following the above procedures and the colored products

were scanned in the wavelength region of 340 to 900nm against reagent blank. The absorbance's for each developed method was recorded and were graphically reported under Fig.-2 for Method-I and Fig. -3 for Method-II respectively.

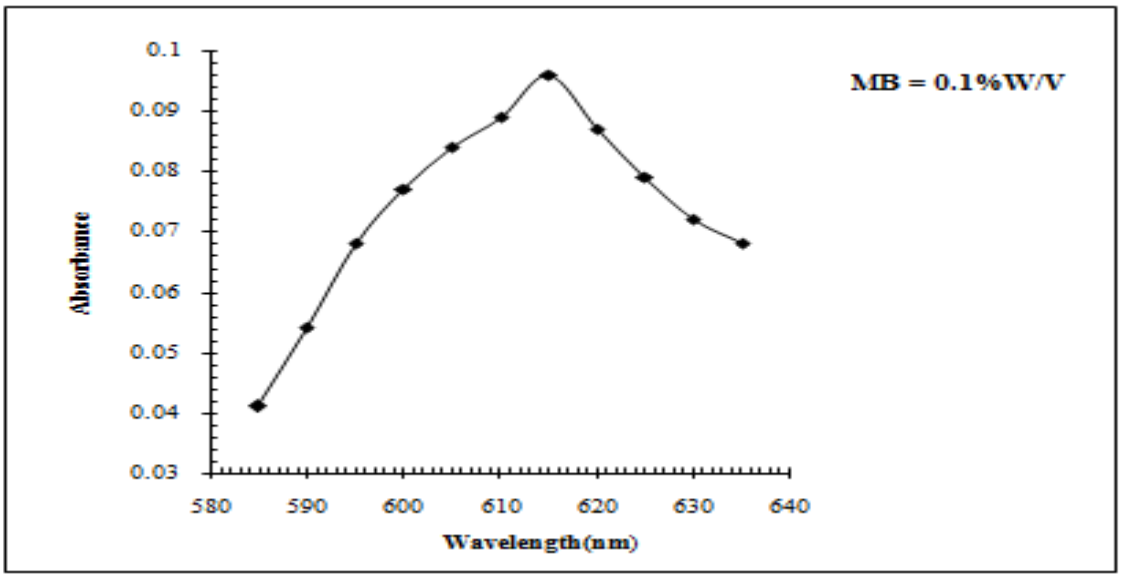

Fig.-2: Absorption spectra of solifenacin succinate for Method-I

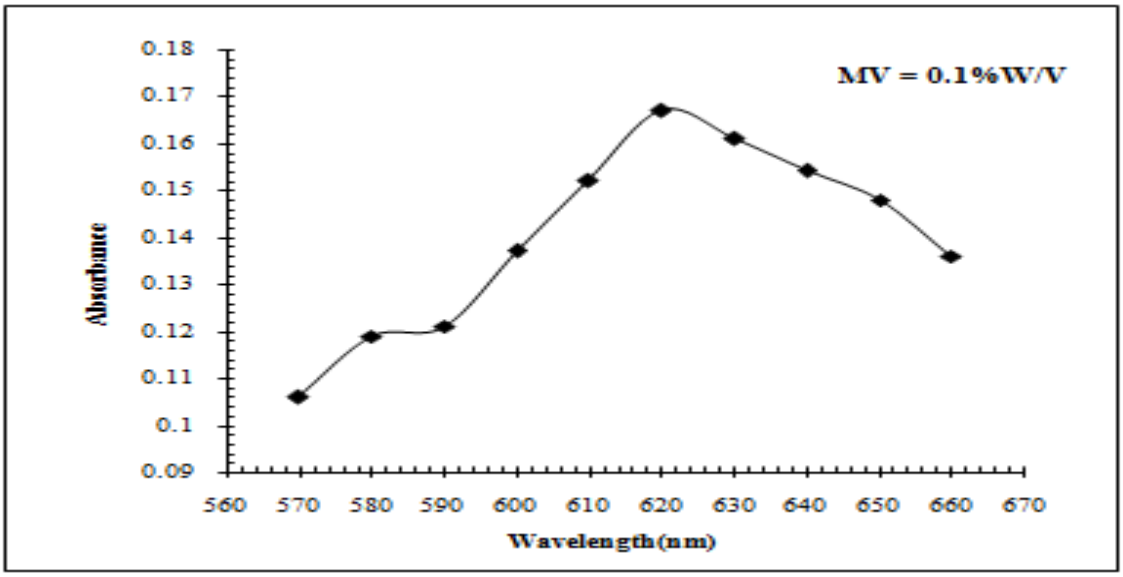

Fig.-3: Absorption spectra of solifenacin succinate for Method-II

Optical Characteristics

Standard solutions containing solifenacin succinate in each linearity level were prepared and were analyzed at their maximum absorption (λ_{max}) for each developed method. Calibration graphs were obtained by plotting absorbance obtained versus the concentration of the drug and their results were deduced by least squares regression analysis. The Beer's law plots of solifenacin succinate in each developed method were recorded graphically (Fig.-4 and 5) and their spectral results [i.e, slope, intercept, correlation, Beer's law limits, molar absorptivity, Sandell's sensitivity and optimum photometric range] were calculated and are reported in Table-2 respectively. The LOD and LOQ values for solifenacin succinate for the developed methods were determined and are reported in Table-2.

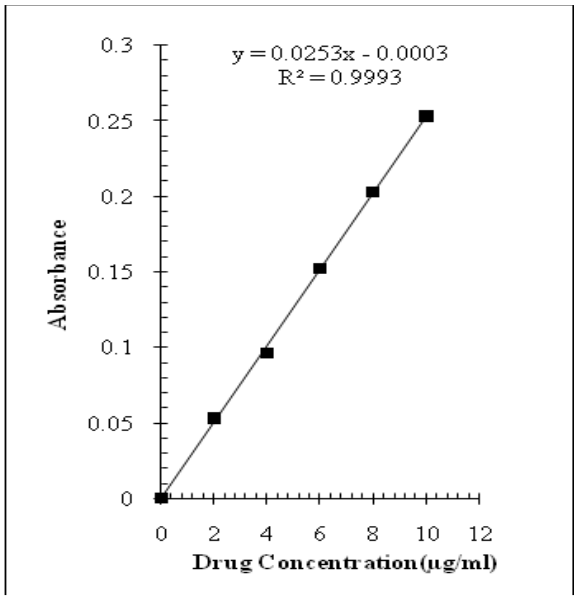

Fig.-4: Beer's law spectra of solifenacin succinate for Method-I

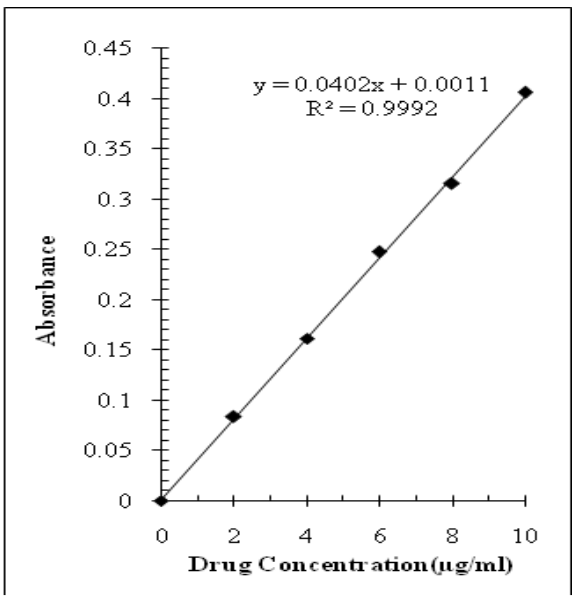

Fig.-5: Beer's law spectra of solifenacin succinate for Method-II

Precision

The precision for the two developed methods (I and II) was evaluated from the absorbance's values obtained by assaying of six replicates of a fixed amount of solifenacin succinate working standard solution in total solution. The percent of relative standard deviation and percent range of error (at 0.05 and 0.01 confidence limits) were calculated and are represented in Table-2.

Accuracy

The accuracy of the proposed methods (I and II) was determined by analyzing different amounts of bulk samples of solifenacin succinate within the Beer's law limits and the percentage of analyte recovered. The accuracy results (percent error) for the two developed methods were reported in Table-2.

Table-2: Results of optical and regression parameters of the proposed methods (I and II)

Parameter	Method-I	Method-II
λ_{max} (nm)	615	620
Beer's law limits (µg/mL)	2.0 – 10.0	2.0 – 10.0
Molar absorptivity (1 $mol^{-1}.cm^{-1}$)	7.164 x 10^3	1.201 x 10^4
Sandell's sensitivity (µg.cm^{-2}/0.001 absorbance unit)	0.3466	0.2917
Optimum photometric range (µg/mL)	3.0 – 9.0	3.5 – 8.5
Regression equation (Y=a+bc) ;slope(b)	0.0253	0.0402
Intercept (a)	0.0030	0.00112
Correlation Coefficient (r)	0.9993	0.9992
Standard Deviation on Intercept (S_a)	0.00344	0.00478
Standard Deviation on Slope (S_b)	0.000518	0.000721
Standard error on Estimation (S_e)	0.00328	0.00456
LOD(µg/mL)	0.407	0.364
LOQ(µg/mL)	1.35	1.18
Relative Standard Deviation (%)*	1.067	1.165
0.05 level	0.892	0.974
0.01 level	1.320	1.441

* Average of six determinations

Analysis of Market Formulations

Commercial formulation (BISPEC tablets-10mg) of solifenacin succinate was successfully analyzed by the two new proposed methods. The values obtained for formulations by the proposed methods were compared statistically with F and t-test with the reported method[7] and was found no significant difference respectively and the results were incorporated in Table-3 for the developed methods.

Table-3: Assay of solifenacin succinate in commercial dosage forms

Method	Pharmaceutical Formulation	Labeled Amount (mg)	PROPOSED METHOD			Reference Method[7] ±S.D	% Recovery obtained **
			Amount Found* (mg) ±S.D	t - (value)	F (Value)		
Method-I	Oral Tablet	10	9.98±0.124	1.118	2.254	9.99±0.186	99.49%
Method-II			9.99±0.147	0.593	1.597		100.00%

*Average ± standard deviation of six determinations; t and F- values refer to the comparison of the proposed method. Theoretical values at 95 % confidence limits t = 2.365 and F = 4.88; ** Average of six determinations.

Chemistry of colored species

The assumed reaction mechanism of the colored species formed in each proposed method has been presented in respective schemes given below.

Method-I and II

The carboxylate anion (negative charge) of solifenacin succinate is expected to attract the positive charge of methylene blue/ and Methylene Violet that behaves as a single unit (Ion-association complex) held together by electrostatic attraction (Figure-6) forming a colored complex that is measured spectrophotometrically.

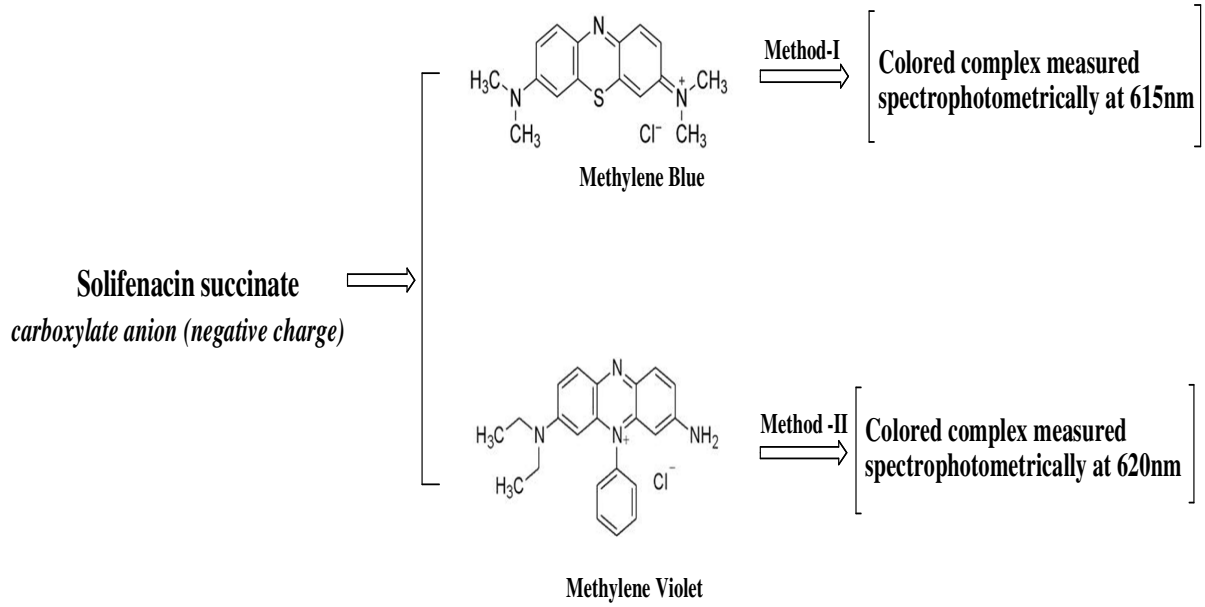

Fig.--6: Reaction analogy of solifenacin succinate with MB(Method-I) &MV(Method-II)

CONCLUSION

Two new direct visible spectrophotometric methods (Method-I and II) were developed and validated for the estimation of Solifenacin succinate in oral tablets as per ICH guidelines. The developed methods (I and II) resulted in linearity in the range of 2-10µg/ml with precision exemplified by relative standard

deviation of 1.067 and 1.165% and with percentage mean recoveries in the range of 99.49 and 100.0% respectively. Basing on the validation results (Table-2) the proposed visible spectrophotometric methods can be used as substitute methods in the routine assay of solifenacin succinate in oral dosage formulations.

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