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Solifenacin succinate estimation in bulk and pharmaceutical preparations by visible spectrophotometry

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ABSTRACT

Two simple, sensitive and cost effective visible spectrophotometric methods (M_1-M_2) were described for the estimation of Solifenacin succinate in bulk and dosage forms. Method M_1 involves Internal salt formation of aconitic anhydride, dehydration product of citric acid [CIA] with acetic anhydride [Ac_2O] to form colored chromogen with an absorption maximum of 580 nm without using any puffer solution and the method M_2 is based on the formation of green colored coordination complex by the drug in free base with cobalt thiocyanate which is quantitatively extractable into nitro benzene with an absorption maximum of 625 nm. Beer's law obeyed in the concentration range of 16-48µg/ml and 20-100 µg/ml for methodM_1 and M_2 respectively. Commercial tablets were analyzed and the results are statistically compared with those obtained by the reference UV method and validated by recovery studies. The results are found satisfactory and reproducible. No interference was observed from the usually existing additives in pharmaceutical formulations.

KEYWORDS

Anti-muscarinic agent;
Assay;
Acetic anhydride;
Citric acid;
Cobalt thiocyanate;
Regression equation.

INTRODUCTION

Solifenacin succinate (SFS) Figure 1 is a urinary antispasmodic of the anti muscarinic class and competitive cholinergic receptor (M_3subtype) antagonist[1]. It is used in the treatment of overactive bladder with or without urge incontinence. It is chemically designated as 1-azabicyclo [2.2.2] oct-3yl (1S)-1-phenyl-3,4-dihydro-1H-isoquinoline-2-carboxylate.Its empirical formula is $C_{23}H_{26}N_2O_2.C_4H_6O_4$ representing molecular weight of 480.55. It is a white or pale yellowish white crystalline powder that is freely soluble in water methanol, dimethyl sulphoxide and glacial acetic acid. SFS acts by relaxing the involuntary detrusor muscle in the wall of the bladder by blocking muscarinic/cholinergic receptors present on the surface of the muscle cells and thus prevents acetylcholine from acting on these receptors.

In literature, several analytical methods such as HPLC[2-6], UPLC[7], semi-micro HPLC[8], HPTLC[10,11], LC-MS/MS[12,13], UV[14,15] and visible[16-18] spectrometric have been reported for the determination of SFS in biological fluids and formulations. The analytical functional present in the drug not fully ex-

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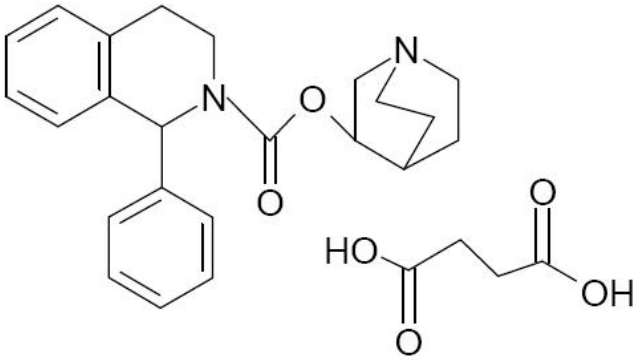

Figure 1 : Chemical structure of solifenacin succinate

ploited. Nevertheless, there still exists a need for development of sensitive accurate and flexible visible spectrophotometric methods for the determination of SFS in pharmaceutical preparations. The authors have made some attempts in this direction and succeeded in developing two methods based on the reaction between the drug and citric acid-acetic anhydride reagent[19] (M_1) or drug and cobalt thiocyanate[20] (M_2). These methods can be extended for the routine quality control analysis of SFS in formulations.

APPARATUS AND CHEMICAL

A Milton Roy UV/Visible spectrophotometer model-1201 with 10mm matched quartz cells was used for all spectral measurements. Systronics model-362 pH meter was used for all the pH measurements. All the chemicals used were of analytical grade. Citric acid monohydrate (Prepared by dissolving 1.2 grams of (1.2%, $6.245X10^{-2}$M) Citric acid in 5 ml methanol initially followed by dilution up to 100ml with acetic anhydride) and Acetic anhydride (SD Fine chemicals), CTC ($2.50x10^{-1}$M, solution prepared by dissolving 7.25 g of cobalt nitrate and 3.8 g of ammonium thiocyanate in 100ml distilled water), Citrate buffer pH(2.0) (prepared by mixing 306ml of 0.1M tri sodium citrate with 694ml of 0.1M HCl and pH was adjusted to 2.0) were prepared.

PREPARATION OF STANDARD AND SAMPLE DRUG STOCK SOLUTION

An accurately weighed quantity of SFS (pure or tablet powder) equivalent to 100mg was mixed with 5ml of 10% Na_2CO_3 solution and transferred into 125ml separating funnel. The freebase released was extracted with 3x15ml portion of chloroform and the combined chloroform layer was brought up to 100ml with the same solvent to get 1mg/ml SFS drug stock solution in free base form. This free base stock solution was further diluted step wise with the same solvent to get the working standard solution concentrations [M_1-400 µg/ml, M_2-500 µg/ml].

ANALYTICAL PROCEDURES

Method M_1

Aliquots of standard SFS drug solution [1.0-3.0ml; 400µg/ml in free base form] in chloroform were taken into a series of 25ml graduated tubes and gently evaporated in a boiling water bath to dryness. To this, 10ml of citric acid- Acetic anhydride reagent was added and the tubes were immersed in a boiling water bath for 30 minutes then the tubes were cooled to room temperature and made up to the mark with acetic anhydride. The absorbance of the colored solutions was measured after 15minutes at 580 nm against the reagent blank (within the stability period of 15-60min.The amount of SFS was in the sample solution computed from its calibration graph Figure 2.

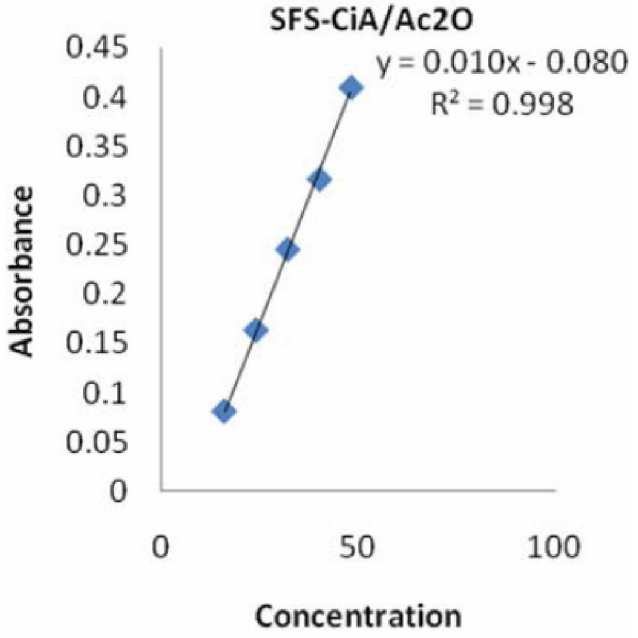

Figure 2 : Calibration graph of SFS-CiA/AC_2O system

Method M_2

Aliquots of standard SFS solution (1.0ml-5.0ml, 500µg/ml in free base form) were delivered into a se-

ries of 125ml separating funnels. Then 2.0ml of buffer solution (pH 2.0) and 5.0ml CTC solution were added. The total volume of aqueous phase in each separating funnel was adjusted to 15.0ml with distilled water. To each separating funnel 10.0ml of nitrobenzene was added and contents were shaken for 2 minutes. The two phases were allowed to separate and absorbance of nitrobenzene layer was measured at 625nm against a similar reagent blank. The colored product was stable for 1 hour. The amount of SFS in the sample solution was computed from its calibration graph Figure 3.

In developing these methods, systematic studies of the effects of various parameters were undertaken by varying one parameter at a time and controlling all others fixed (OVAT method). The effect of various parameters such as time, volume and strength of reagents, pH buffer solution and order of addition of reagents, stability period and solvent for final dilution of the colored species were studied and the optimum conditions were established. Among the various water immiscible organic solvents (C_6H_6, $CHCl_3$, dichloro methane, nitro benzene, chloro benzene and CCl_4) tested for the extraction of colored coordinate complex into organic layer, nitrobenzene was preferred for selective extraction of colored complex from organic phase in method M_2. Different solvents like acetic anhydride, acetic acid, methanol, ethanol and isopropanol were also used as diluents but acetic anhydride was found to be ideal for final dilution in method M_1. The ratio of organic to aqueous phase was found to be 1:1.5 by slope ratio method for method M_2. The optical characteristics such as Beer's law limit, Sandell's sensitivity, molar absorptivity, percent relative standard deviation, (calculated from the six measurements containing 3/4th of the amount of the upper Beer's law limits) were calculated and the results are summarized in TABLE 1.

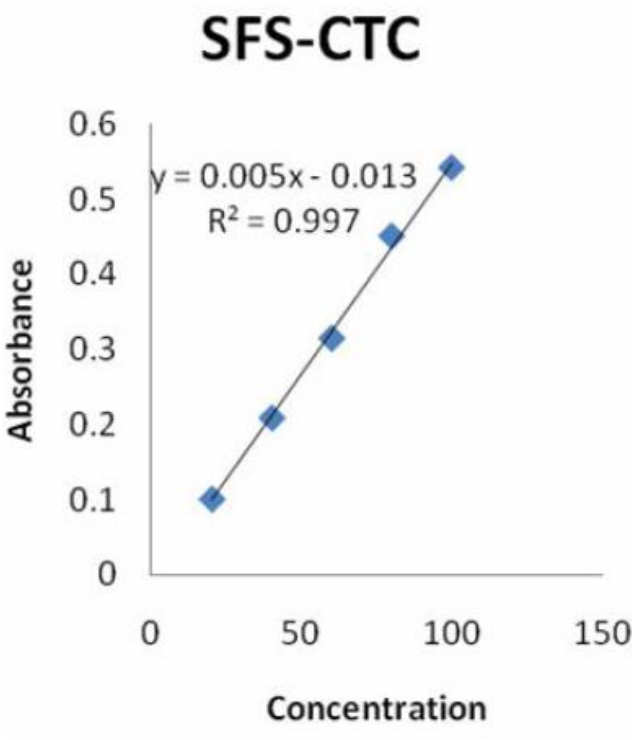

Figure 3 : Calibration graph of SFS-CTC system

Commercial formulations containing SFS were successfully analyzed by the proposed methods. The values obtained by the proposed and UV reference methods for formulations were compared statistically by the t-and F-test and found not to differ significantly. As an additional demonstration of accuracy, recovery experiments were performed by adding a fixed amount of the drug to the pre analyzed formulations at three different concentration levels. These results are summarized in TABLE 2.

Recovery experiments indicated the absence of interference from the commonly encountered pharmaceutical excipients present in formulations. The proposed methods are found to be simple, sensitive and accurate and can be used for the routine quality control analysis of SFS in bulk and formulations.

TABLE 1 : Optical characteristics, precision and accuracy of the proposed methods

Parameters	Method M_1	Method M_2
λ_{max}(nm)	580	625
Beer's law limit (µg/ml)	16- 48	20-100
Sandell's sensitivity (µg/cm^2/0.001 abs. unit)	0.00522449	0.007619048
Molar absorptivity (Litre/mole/cm)	91980.27344	63072.1875
Regression equation (Y) *= a +b x		
Intercept (a)	-0.080	-0.013
Slope (b)	0.010	0.005
Correlation coefficient	0.998	0.997
%RSD	1.84	1.64
% Range of errors (95% Confidence limits)	1.93	1.72
0.05 significance level 0.01 significance level	3.0	2.7

***Y = a + b x, where Y is the absorbance and x is the concentration of SFS in µg/ml**

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TABLE 2 : Analysis of SFS in pharmaceutical formulations

Method	*Formulations	Labeled Amount (mg)	Found by Proposed Methods			Found by Reference Method ± SD	#% Recovery by Proposed Method ± SD
			**Amount found ± SD	t	F		
M_1	Batch-1	5	4.94±0.058	0.91	3.1	4.95±0.033	98.82±1.15
	Batch-2	5	4.96±0.018	1.05	4.16	4.97±0.009	99.15±0.37
M_2	Batch-1	5	4.95±0.026	0.287	1.59	4.95±0.033	98.96 ±0.52
	Batch-2	5	4.96±0.017	0.52	3.61	4.97±0.009	99.22±0.35

*** Batch- 1 and Batch-2: tablets of Bispec (Dr Reddy) Solifen(Ranbaxy); **Average ± Standard deviation of six determinations, the t- and f-values refer to comparison of the proposed method with UV reference method. Theoretical values at 95% confidence limits t =2.57 and F = 5.05. # Recovery of 10mg added to the pre analyzed sample (average of three determinations). Reference method (reported UV method) using distilled water (λ_{max}=220nm)**

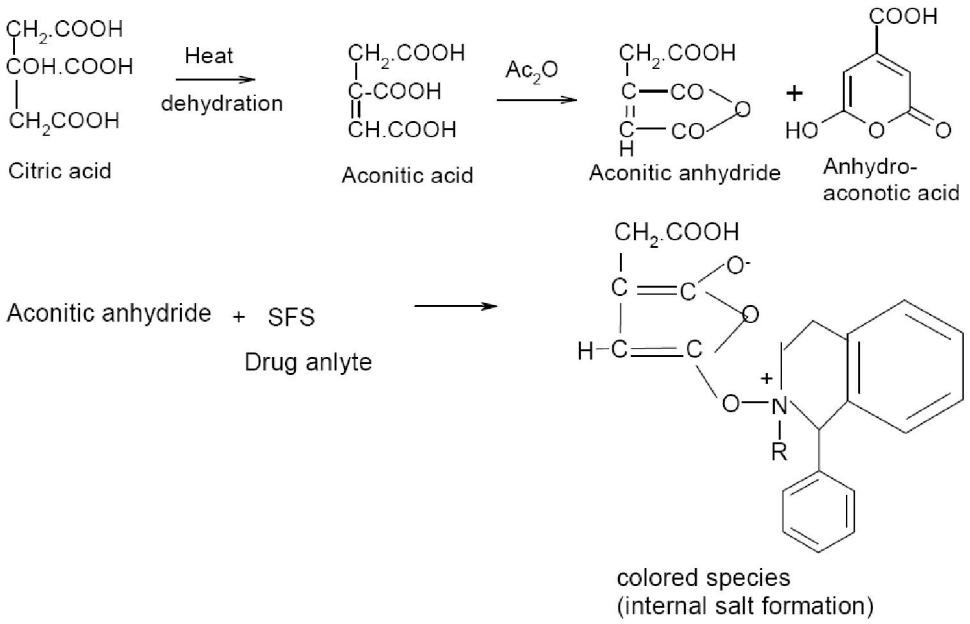

Figure 4 : Probable scheme for method M_1

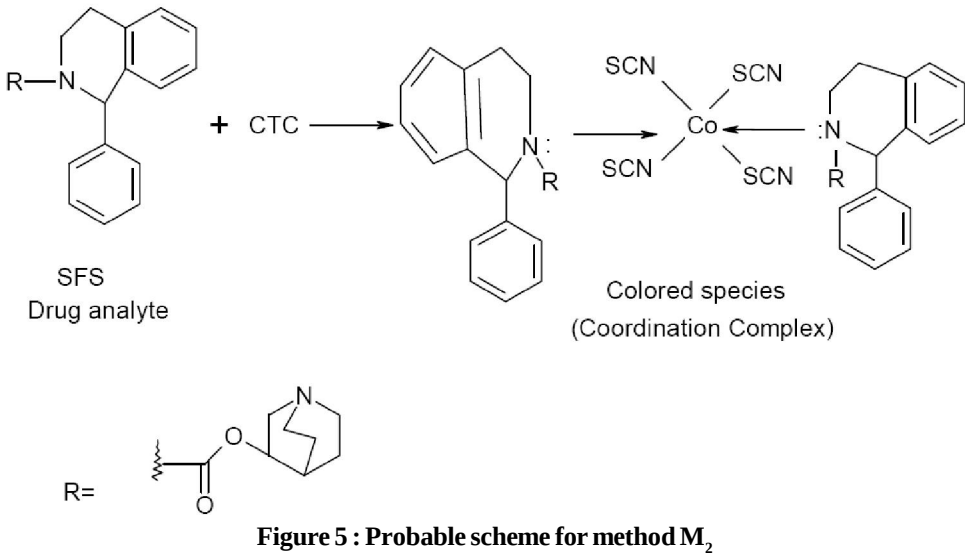

Figure 5 : Probable scheme for method M_2

Chemistry of colored species

In method M_2 the green color species formation is the coordination complex of the drug (electron donor) and the central metal of cobalt thiocyanate, which is

extractable into nitro benzene from aqueous solution and in method M_1 red-violet color internal salt of aconitic anhydride is formed when SFS was treated with CTC or CIA/Ac_2O reagents. The formations of colored species are due to the presence of the cyclic tertiary nitrogen in it. It is based on the analogy of tertiary amine as given in scheme (Figure 4&5).

CONCLUSION

The reagents utilized in the proposed methods are normal cost, readily available in all laboratories and small scale pharmaceutical industries and the procedures do not involve any critical reaction conditions or tedious sample preparation. The proposed methods can be used as alternative methods to reported ones and provide wide choice for the routine determination of the SFS depending upon the availability of chemical and situation arising due to the presence of concomitants.

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