Visible Spectrophotometric Methods for the Determination of Sildenafil in Pharmaceutical Formulations

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Two visible spectrophotometric methods have been developed for the estimation of sildenafil in pure and in pharmaceutical formulations. First developed visible spectrophotometric method was based on formation of yellow coloured chromogen with sodium nitropruside and hydroxylamine hydrochloride which showed absorbance maximum at 475 nm and Beer's law was obeyed in the concentration range of 40-200 μg/ml and second developed method was based on formation of violet coloured chromogen with metol and iodine which showed maximum absorbance at 520 nm and Beer's law was obeyed in the concentration range of 160-280 μg/ml. Results of analysis for both the methods were validated statistically and by recovery studies.

Sildenafil, (SDF) [(1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-H-pyrozolo-[4,3-d] pyrimidin-5-yl) phenyl sulphonyl]-4-methyl piperazine[1-2], is indicated for the treatment of erectile dysfunction in men. It is a new drug and is not official in any of the pharmacopoeia. Literature survey revealed two reverse phase HPLC[3,4] methods available for its determination. No spectrophotometric method has so far been reported. As a part of our continuing efforts to develop simple, sensitive and selective visible spectrophotometric analytical procedure for bulk drugs and their formulations, attention was focused on SDF molecule, keeping in view the relative lack of such methods for its estimation. This paper describes two simple spectrophotometric methods for SDF using sodium nitropruside and hydroxylamine hydrochloride for the first method and metol, iodine and sulphanilic acid for the second method.

In the first method, SDF is reduced with sodium nitroprusside and coupled with hydroxylamine hydrochloride to yield a coloured chromogen. In the second method, metol is used. Metol (p-N-methyl amino phenol sulphate) is a versatile chromogenic reagent capable of reacting with different functional groups under different conditions enabling the estimation of many pharmacodynamic agents belonging to different classes[5]. Metol is a bifunctional substrate, when treated with an oxidising agent, it under goes oxidization with two electron transfers to yield the very unstable and highly reactive p-N-methyl benzoquinone monoamine. Sildenafil was allowed to react with excess of the oxidising agent and the excess was then determined directly after release of iodine from potassium iodide with metol-sulphanilic acid. The above two methods for the determination of SDF in pure drug and in pharmaceutical formulations were applied.

A Elico SL 171 spectrophotometer with 1 cm matched quartz cell and Elico LI-120 digital pH meter were used. All the chemicals used were of analytical grade and all the solutions were prepared in double distilled water. Freshly prepared solutions were used. Solution of sodium nitroprusside (5% w/v), hydroxylamine hydrochloride (5% w/v) and sodium carbonate (10% w/v) were prepared in distilled water.

Iodine (0.089% w/v) was prepared in distilled water, potassium iodide (0.83% w/v) was added and shaken well. Metol (2% w/v) was prepared in distilled water. Sulphanilic acid (0.4% w/v) was prepared by dissolving 400 mg of it in 100 ml distilled water. HCl (1 M) was prepared from concentrated hydrochloric acid by suitable dilution. Working standard solution of SDF was prepared by dissolving 100 mg of SDF in 100 ml distilled water to get a 1 mg/ml stock

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solution and this stock solution was diluted with distilled water to obtain the working standard solution.

To a series of 10 ml, volumetric flasks, aliquots of standard drug solution ranging from 0.4 to 2 ml were added. This was followed by the addition of 1.2 ml sodium nitroprusside and 2.4 ml of hydroxylamine hydrochloride. To the resultant solution, 1.2 ml of sodium carbonate was added and the volume was made upto 10 ml with distilled water. The solutions were shaken for 15 min. An yellow coloured chromogen was obtained, which was measured at 475 nm against the reagent blank.

Aliquots of standard drug solutions ranging from 1.6 to 2.8 ml of stock solutions were taken in 10 ml volumetric flasks, 1.5 ml of hydrochloric acid and 2 ml of iodine solution were added. The solutions were allowed to stand for 15 min. Then the solutions were centrifuged for 5 min. The precipitates formed were separated by filtration. These precipitates were washed with 10 ml distilled water. To 3 ml of this resultant filtrate, 3 ml metol and 1.5 ml sulphanilic acid were added and volume made upto 10 ml with distilled water. The absorbance of violet coloured chromogen was measured at 520 nm against the reagent blank after 15 min.

Three different brands of SDF formulations were taken for analysis. The average weight of each formulation was calculated by using 20 tablets. The formulation equivalent to 100 mg was transferred into 100 ml volumetric flask. To the flask, 10 ml distilled water was added and shaken for 5 mm. Final volume was made upto 100 ml with distilled water so as to get a 1 mg/ml stock solution. From this stock solution aliquots containing required concentrations of the drug were taken for analysis. The estimation of drug from formulations was done in a similar way that was reported for pure drug.

The amount of SDF present in each sample analysed was computed from the calibration curve. The optical characteristics and the precision data of the proposed methods have been calculated and presented in Table 1. These methods were also applied for analysing SDF in tablets. To evaluate the validity and reproducibility of the proposed methods, known amount of pure drug was added to a previously analysed pharmaceutical formulations (tablets) and the mixtures were again analysed. The percentage recovery data of the drug by these methods have been given in Table 2. Interference studies revealed that excipients and additives commonly present in tablets do not interfere with the determinations. These results indicate that the proposed methods are sensitive, accurate and precise and can be used for the routine determination of SDF in bulk and in dosage forms.

TABLE 1: OPTICAL CHARACTERISTICS AND PRECISION DATA.

Parameters	Method	
	A	B
λ_{max} (nm)	475	520
Beer's Law limits (μg/ml)	40-200	160-280
Sandell's sensitivity ($\mu g/cm^2/0.001$ A.U.)	3.51×10^{-2}	3.571×10^{-2}
Molar extinction coefficient (l/mol.cm)	1.911×10^{4}	1.898×10^{4}
Correlation coefficient	0.9999	0.9999
Regression equation (b+ac)		
Slope (a)	1.127×10^{-3}	1.3975×10^{-3}
Intercept (b)	1.1×10^{-3}	0.4222
% relative standard deviation	0.4097	0.6196
% range of error		
Confidence limit with 0.05 level	0.6298	0.6498
Confidence limit with 0.01 level	0.9254	1.0165

TABLE 2: ASSAY OF SILDENAFIL IN TABLETS.

Pharmaceutical preparation	Labelled amount (mg)	Amount found in mg*		% Recovery**
		A	B	
Sample I (Pure drug)	25	24.9	24.92	99.8
Sample II (Tablet)	50	49.9	49.9	99.9
Sample III (Tablet)	100	99.8	99.9	99.9

*Average of six determinations. **After adding 500 μg: each value is an average of three determinations.

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Controlled Release of Glipizide from Ethylene Vinyl Acetate Microcapsules

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An industrially feasible technique of microencapsulation by ethylene vinyl acetate copolymer and the resulting microcapsules were investigated. Ethylene vinyl acetate microcapsules of glipizide were prepared by an emulsion solvent evaporation method employing various proportions of coal and core materials and chloroform as solvent for the polymer ethylene vinyl acetate. The microcapsules are spherical, discrete, free flowing and monolithic, multinucleate type. Microencapsulation efficiency was in the range of 89-97%. Glipizide release from the microcapsules was slow and extended over more than 12 h and depended on coat:core ratio, wall thickness and size of the microcapsules. Drug release was diffusion controlled and followed zero order kinetics after a lag period of 1 h. Good linear relationships were observed between wall thickness and release rate and T_{50} (time for 50% release) values. Release from some of the microcapsules was very close to that from a commercial SR tablet formulation of glipizide.

Microencapsulation by various polymers and their applications are described in standard text books[1,2]. Ethylene vinyl acetate copolymer (EVA) is copolymer of ethylene and vinyl acetate. Though EVA has good film forming properties[3,4], its potential in microencapsulation has not been investigated. No reports are available on microencapsulation by EVA copolymer. In a few reports[5,6] monolithic systems, composed of ethylene vinyl acetate copolymer have been studied for the controlled delivery of macromolecular drugs such as insulin and heparin. In these studies, the drug and polymer solution were mixed together and cast as a film on a precooled plate to yield a matrix device in the form of a slab, which could be further divided into 1x1 cm squares. In the present work an industrially feasible technique of microencapsulation by EVA copolymer was developed and the resulting EVA microcapsules were investigated. Glipizide, an effective antidiabetic which requires controlled release owing to its short biological half life of 3.4±0.7 h was microencapsulated by EVA and the resulting microcapsules were studied. A few sustained release formulations of glipizide (10 mg) are available commercially.

Glipizide was a gift sample from M/s. Micro Labs Ltd., Pondicherry. Ethylene vinyl acetate copolymer (Grade1408) was procured from M/s Polyolefins Industries Ltd., Mumbai. Chloroform GR (Merck) and sodium carboxymethylcellulose (sodium CMC with a viscosity of 1500-3000 cps of a 1% w/v solution at 25°, Loba-Chemie) were procured from com-

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