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NEW SPECTROPHOTOMETRIC METHOD FOR THE DETERMINATION OF FLUTAMIDE IN PHARMACEUTICAL PREPARATION USING CHROMOTROPIC ACID AS A COUPLING AGENT

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Abstract

A rapid, selective, sensitive spectrophotometric method for the determination of flutamide (FLA) is described by the interaction of reduced flutamide in presence of potassium ferricyanide ($K_3[Fe(CN)_6]$) with chromotropic acid in basic medium. Absorbance of the resulting chromophore is measured at 465 nm and is stable for more than 7 days. The method is successfully employed for the determination of flutamide in pharmaceutical preparations, and common excipients, used as additives in pharmaceuticals, do not interfere in the proposed method. The method offers the advantages of simplicity, rapidity and sensitivity without the need for extraction.

Introduction

Flutamide[1] (FLA) is widely used as an antiandrogen drug. It is also used for prosthetic cancer. It is chemically known as2-methyl-N- [4-nitro-3-(trifluoromethyl)phenyl] propanamide. This drug and its primary hydroxy metabolite are non-steroidal at the target cells in the secondary sex organs, but also decrease the metabolism of C-19 steroids by the cytochrome p-450 system[2]. FLA, recently included in the United States Pharmacopoeia involves chromatographic method[3], polarography[4], gas-chromatography[5], and high performance liquid chromatography[6]. The polarographic, U.V. spectro-photometric and HPLC determination of FLA in tablets has been reported[7]. Other spectrophotometric methods available for the determination of FLA include the formation of yellow colour with HCl[8], promethazine hydrochloride or resorcinol or NEDA N-(1-naphthyl) ethylenediamine dihydrochloride[9], p-dimethylamino cinnamaldehyde or NEDA or chromotopic acid or resorcinol[10].

The authors have made some attempts in this direction, and succeeded to develop a new reagent, namely chromotropic acid in presence of alkaline oxidising agent ($K_3[Fe(CN)_6]$). The method offer the advantages of sensitivity, selectivity, rapidity and more stability when compared to other existing method without any need for extraction.

Experimental

Apparatus

A JASCO Model UNIDEC-16 UV-VIS Spectrophotometric with 1:0 cm matched cells was used for electronic spectral measurements.

Reagents

All chemicals and solvents used were of analytical reagents grade. Deionized water was used to prepare all solutions and in all experiments. Commercial dosage forms were purchased from local sources.

Accurately weighed 50 mg FLA was transferred to a 100 ml beaker containing 4.0 ml of concentrated methanol, 0.5 g Zn dust and 1.0 ml of concentrated hydrochloric acid, the mixture is left for 30 min till the reaction ceases. Solution was filtered in to 100 ml standard flask and made up to mark. A working standard solution of FLA containing 50 µg ml^{-1} was prepared by further dilution. 0.2% solution of chromotropic acid was prepared freshly by dissolving 200 mg in 100 ml deionised water. 3% potassium ferricyanide solution is prepared a freshly by dissolving 3 g of $K_3[Fe(CN)_6]$ is distilled water and made up to 100 ml. 2% solution of NaOH was used for the experiments.

Procedure

Aliquots of working standard solution of reduced FLA 20 µg were transferred in to 250 ml calibrated flask, 2 ml of 0.2% freshly prepared chromotropic acid was added, followed by the addition of 1.5 ml of 3% potassium ferricyanide an oxidising agent along with 2% NaOH until the medium is basic (pH 10). After mixing the solution thoroughly, the absorbance was measured at 465 nm against the corresponding reagent blank.

For Pharmaceutical Formulations

Twenty tablets were powdered and thoroughly mixed. A powdered tablet, equivalent to 50 mg, was dissolved in 50 ml of concentration HCl and filtered. The working standards were prepared by suitable dilution and the standard procedure was followed for the determination of FLA in tablets.

Results and Discussion

Spectral Characteristics

A chromophore product in a basic medium (HCl) was obtained when reduced FLA was added to the chromotropic acid in presence of oxidising agent ($K_3[Fe(CN)_6]$) with a ? $_{max}$ 465 nm. The stability of the complex was more than 7 days.

Optimization of Reagent Concentration

Various concentrations and volume ranges for all the reagents were studied in detail. It was found that chromotropic acid in the range of 2-4 ml, potassium ferricyanide in the range of 1-2 ml and sodium hydroxide in the range of 1-3 ml were necessary to obtain a stable coloured product with maximum colour intensity.

Optimum Conditions for Stability of Complex

The coloured product of FLA formed by the proposed method was found to be stable for more than 7 days at room temperature. Reproducible results were obtained in the temperature range of 20-40^{0}C. An increase in temperature of above 40^{0}C and below 15^{0}C were decreased the absorbance data, indicating the decomposition of product. 28-37^{0}C is recommended for the absorbance measurements.

Optical Characteristics

In order to test whether the red product formed obeys Beer's law or not, the absorbance of a series of solution containing varying amounts of FLA were recorded against the reagent blank at 465 nm.

Beer's law limits, molar absorptivity, specific absorptivity, Sandell's sensitivity and optimum range by photometric determinations. The slope, the intercept and the correlation co-efficient were evaluated by least-squares regression analysis are presented in Table 1.

Table 1 : Optical Characteristics

Parameters	Proposed Method
Colour	Orange red
? $_{max}$	465 nm
Stability	more than 7 days
Beers law (µg ml^{-1})	0.1 µg to 12 µg
Limit of detection (µg ml^{-1})	0.1316
Molar absorbitivity (1 mol^{-1} cm^{-1})	0.309 H 10^5
Sandell? s sensitivity (µg cm^{-2})	0.0123
Optimum photometric range (µgml^{-1})	0.8 to 10
Regression equation (y)[a]	
Slope (b)	0.0396
Intercept (a)	0.0017
Correlation co-efficient (r)[b]	0.9960

Relative standard deviation[c] (%)	
Range of error	1.06

ay = ax + b, where ? x? is the concentration in µg ml^{-1}

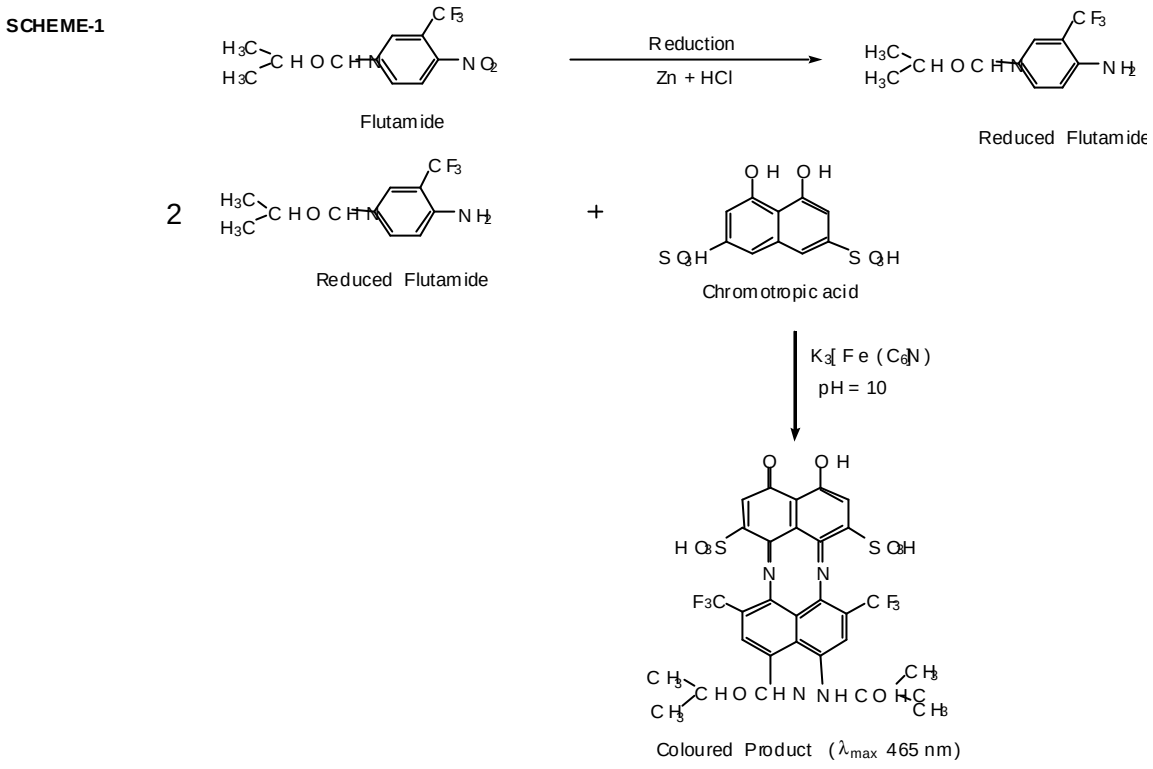
bn = 10

c Ten replicates

Reaction Sequence

The chromotropic acid reacts with reduced FLA in presence of oxidising agent $[K_3(Fe(CN)_6]$ produces wine red coloured product at pH 10 with $?_{max}$ of 465 nm. The reaction mechanism for the formation of product is shown in Scheme-1.

SCHEME-1



Inference

The effect of the concomitant associated with the FLA in the pure form and its formulations were investigated using the developed method. This method does not suffer any interference from commonly associated excipients and additives in the preparation of tablets such as sucrose, lactose, dextrose, starch, talc, stearic acid and sodium alginate. The results are tabulated in Table 2.

Table 2 : Determination of flutamide in presence of excipients

Excipient	Amount of excipient added (mg)	% Recovery[a]
Carboxyl methyl cellulose	45	99.9 " 0.95
Dextrose	30	99.8 " 0.95
Starch	35	99.9 " 0.90
Cellulose	30	99.7 " 0.85
Crumacacia	35	99.8 " 0.90
Lactose	40	99.7 " 0.95
Magnesium stearate	45	100.3 " 0.90
Talc	30	99.7 " 0.90
Sodium alginate	40	99.6 " 0.80
Stearic acid	30	99.8 " 0.85

8 µg ml^{-1} of FLA taken for present study

[a] Average of five determinations

Application

The applicability of the method for the assay of pharmaceutical preparations was examined. The results of assays of available tablets of FLA are summarized in Table 3. These result were accurate and reproducible.

Table 3 : Determination of FLA in pharmaceutical preparations

Drug trade name	Label claim (mg)	Amount of drug found[a] in (mg)	
		Proposed method	Reported method
Cytomid[b]	250	249.3 " 0.80	249.2 " 0.75
Drogenil[c]	250	249.7 " 0.95	249.5 " 0.90
Flutacare[d]	250	249.5 " 0.95	249.4 " 0.90
Plutamide[e]	250	249.8 " 0.85	249.6 " 0.80
Prostamide[f]	250	250.9 " 0.90	250.7 " 0.95

[a] Average of five determinations
[b] Marketed by Cipla
[c] Marketed by Fulford
[d] Marketed by Criticare
[e] Marketed by Torrent
[f] Marketed by BDH

Conclusion

The results clearly indicate the utility of the proposed method for the analysis of FLA in pure and dosage form in pharmaceutical preparations. The rapid colour development, excellent Beer's Law curve and reproducibility as well as freedom from interference by the foreign ions are advantageous of this method. This method requires neither extraction nor heating.

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