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EXPERIMENTAL EVALUATION OF FLUTAMIDE DRUG USING SODIUM SALICYLATE HYDROTROPE

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ABSTRACT

Flutamide is an antiandrogen drug which is sparingly soluble in water. It is primarily used to treat prostate cancer. A novel, safe and sensitive method of titrimetric estimation has been developed using 2 M sodium salicylate as a hydrotropic solubilizing agent for the quantitative determination of Flutamide. There was more than a 27-fold enhancement in aqueous solubility of Flutamide in 2 M sodium salicylate solution. The results of analysis obtained by the present method are comparable with that by the Indian Pharmacopoeial Method. The present method is new, simple, accurate and reproducible. Results of the analysis were validated statistically. Statistical data proved the accuracy, reproducibility and precision of the present method.

INTRODUCTION

Poor solubility has become a major challenge in drug delivery as 90% of the active ingredients have at least some solubility issues this proportion is still growing. This implies that drug solubilization techniques could potentially impact up to 90% of R&D. Flutamide and other anti-androgens work by stopping testosterone from reaching the cancer cells. Without testosterone the Prostate cancer cells are not able to grow. It is well known that drug efficiency can be severely limited by poor aqueous solubility. The most common side effects of Flutamide are mild liver injury, which resolves when the drug is discontinued. It may also cause gastrointestinal side effects, Itchy skin, yellowing of the skin, unusual flu-like symptoms. The ability to increase aqueous solubility can thus be a valuable aid to increase efficacy or to reduce side effects for certain drugs. Special techniques are required to solubilize poorly water-soluble drugs. Hydrotropy is one of such techniques [1-4].

This term hydrotropy was originally put forward by Carl Neuberg to describe the increase in the solubility of a solute by the addition of fairly high concentrations of alkali metal salts of various organic acids.[5] However, the term has been used in the literature to designate non-micelle-forming substances, either liquids or solids, organic or inorganic, capable of solubilizing insoluble compounds. Hydrotropes are a class of chemical compounds that cause a several fold increase in the solubility of sparingly soluble solutes under normal conditions. In other words “Compounds that cause increase in aqueous solubility” – termed as Hydrotropes. On the basis of various theoretical and experimental efforts, several mechanisms have been proposed to explain the effects provided by hydrotropes.[6]

Maheshwari et al. have applied the use of hydrotropy in titrimetric and spectrophotometric estimation of a large number of poorly water-soluble drugs, hence discouraging the use of organic solvents. Sodium benzoate, sodium salicylate, sodium ascorbate, sodium glycinate, niacinamide, sodium citrate and urea are the most popular examples of hydrotropic agents that have been used to solubilize a large number of poorly water-soluble compounds. Various organic solvents like methanol, chloroform, alcohol, dimethyl formamide,and benzene have been employed for the solubilization of poorly water soluble drugs for their analysis. Drawbacks of organic solvents include higher cost, toxicity, pollution, and error, in analysis due to volatility [7-15]. The present study aims to apply hydrotropic solution of sodium salicylate as a solubilizing

agent to analyze a sparingly water-soluble drug, flutamide, by titrimetric estimation. There was tremendous increase in solubility of flutamide in 2 M sodium salicylate solution. Hence, it was thought worthwhile to solubilize the drug with the help of sodium salicylate solution to carry out the estimation.

MATERIALS AND METHODS

Analysis of Flutamide drug by I.P. (2007) method:-

Accurately weighed (0.3 g) Flutamide drug was dissolved in 50 ml of ethanol (95%) and 20 ml of distilled water was added. It was titrated against sodium hydroxide solution (0.1 M) using phenol red solution as an indicator until a reddish violet color was obtained. 1 ml of 0.1 M sodium hydroxide is equivalent to 0.01801 g of $C_{11}H_{11}F_3N_2O_3$. Necessary blank runs were carried out to get drug content (Table-1).

Analysis of Flutamide drug by proposed titrimetric method:-

In the proposed method, accurately weighed (0.3 g) Flutamide drug was solubilized in 40 ml of 2 M Flutamide solution in a conical flask by shaking for about 5 min and titrated against sodium hydroxide solution (0.1 M) using phenolphthalein as an indicator until a reddish violet color was obtained. Necessary correction was done by conducting blank runs and amount of Flutamide was calculated (Table -1).

RESULTS AND DISCUSSION

Results of solubility studies of Flutamide revealed that enhancement in solubility in 2 M sodium salicylate solution was more than 27-fold. The results of analysis of Flutamide by proposed titrimetric method are given in Table-I. It is evident from Table-II that the values of mean percent drug (Flutamide) estimated by Indian Pharmacopoeial and proposed titrimetric methods are 96.52 and 98.88 respectively. The results of analysis by the present titrimetric method are comparable to the results obtained from the Indian Pharmacopoeial method. The amounts of drug estimated by Indian Pharmacopoeial and Present Titrimetric Methods are very close to each other and very near to 100.0, indicating the accuracy of the present method of analysis. Low values of standard deviation, percent coefficient of variation and standard error (Table-2), further validated the proposed titrimetric method.

Table 1 - Analysis data of Flutamide drug sample

Amount of Drug Analyzed (mg)	Amount of Drug Found (mg)		% Drug Estimated	
	I.P.M	P.T.M	I.P.M	P.T.M
300	285.28	294.72	95.09	98.24
300	295.63	294.36	98.54	98.12
300	288.42	302.18	96.14	100.72
300	288.95	295.35	96.31	98.45

P.T.M. = Present Titrimetric Method

I.P.M. = Indian Pharmacopoeial Method.

Table 2- Statistical evaluation of analysis of Flutamide drug sample

Method of Analysis	% Drug Estimated	Coefficient of Variation (mean + SD)	Standard Error (%)
I.P.M	96.52±1.451	1.451	0.725
P.T.M	98.88±1.232	1.232	0.616

CONCLUSION

Hence, it can be concluded that the hydrotropic method is new, simple, cost effective, accurate, safe and precise and can be successfully employed in the routine analysis of Flutamide in drug sample. Decisive advantage is that the organic solvent is precluded but not at the expense of accuracy. There is a good scope for other poorly water-soluble drugs which may be tried to get solubilized in 2 M sodium salicylate solution (as hydrotropic agent) to carry out their titrimetric and/or spectrophotometric analysis excluding the use of costlier and unsafe organic solvents. The present method is worth adopting in the respective Pharmacopoeia.

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