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Research Article

QUANTITATIVE ANALYSIS OF THEOPHYLLINE BULK SAMPLE USING SODIUM SALICYLATE HYDROTROPE

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ABSTRACT

Solubilization of poorly water-soluble drugs has been a very important issue in screening studies of new chemical entities as well formulation research. 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 theophylline in bulk, a sparingly water-soluble keratolytic drug. There was more than a 18-fold enhancement in aqueous solubility of theophylline in 2 M sodium salicylate solution. The hydrotrope used in this work is freely soluble in water, non toxic and does not interfere in analysis. The results of analysis obtained by the proposed method are comparable with the results of analysis obtained by the Indian Pharmacopoeial method. The proposed method is new, simple, accurate and reproducible. Results of the analysis were validated statistically.Statistical data proved the accuracy, reproducibility and precision of the proposed method.

Key words: Theophylline, Sodium salicylate, Solubility enhancement, Hydrotropes, Solubilization

INTRODUCTION

The phenomenon of hydrotropy, i.e., the increase in solubility of sparingly soluble compounds in aqueous solutions was first reported by Neuberg. Hydrotropes are "short chain organic compounds with a polar group [that] could serve as agents to dissolve poorly water soluble substances into water, if added in high concentrations." The ability of hydrotropes to increase the solubility of organics in water is often strongest when the hydrotrope concentration is sufficient to induce the formation of associated structures [1]. The concentration at which self association begins is denoted as Minimum Hydrotrope Concentration (MHC) and is often indicated by changes in solution properties such as viscosity, conductivity, surface tension, or solubility [2]. The relatively high concentrations required to reach the MHC, however, often restrict the commercial application of hydrotropes[3]. Despite this extensive study and the numerous commercial and pharmaceutical applications many ambiguities regarding their classification and molecular association still exist [4,5].

On the basis of various theoretical and experimental efforts, several mechanisms have been proposed to explain the effects provided by hydrotropes [6, 7]. The first proposes the formation of a complex between additives and solute, which would then show a higher aqueous solubility [8,9]. Another hypothesis proposes that the hydrotrope changes the structure of liquid water as either "structure breakers" or as "structure makers". A third hypothesis involves the self-association of the additives to form aggregates that may act as micelles, affecting the solubility and properties of the other solute [10]. This proposal is supported by experimental data pointing out that some aromatic sulfonates associate in aqueous solutions[11].

The advantage of certain properties, such as the solvent character being independent of pH, high selectivity, absence of emulsification, inexpensive aqueous phase makes this technique superior to other solubilization methods such as micellar solubilization, miscibility, co-solvency, salting-in, etc[12]. Because of the solubilizing effect of these hydrotropes, the mass transfer coefficient of two-phase systems can considerably be enhanced [13].

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[14]. 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[15]. Drawbacks of organic solvents include higher cost, toxicity, pollution, and error, in analysis due to volatility[16]. The present study aims to apply hydrotropic solution of sodium salicylate as a solubilizing agent to analyze a sparingly water-soluble drug, theophylline, by titrimetric estimation[17]. There was tremendous increase in solubility of theophylline (a widely used keratolytic agent) in 2 M sodium salicylate solution[18, 19]. Hence, it was thought worthwhile to solubilize the drug with the help of sodium salicylate solution to carry out the estimation[20-23].

MATERIALS AND METHODS

Analysis of theophylline bulk sample by I.P. (2007) method

Accurately weighed (0.3 g) theophylline bulk sample was dissolved in 50 ml of ethanol (95%) and 20 ml of distilled water was added. It was titrated with sodium hydroxide solution (0.1 M) using phenol red solution as indicator until a reddish violet color was obtained. 1 ml of 0.1 M sodium hydroxide is equivalent to 0.01801 g of C7H6N4O2. Necessary blank determination was carried out to get drug content (Table-1).

Analysis of theophylline bulk sample by proposed titrimetric method

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

RESULTS AND DISCUSSION

Results of solubility studies of theophylline revealed that enhancement in solubility in 2 M sodium salicylate solution was more than 18-fold. The results of analysis of theophylline by proposed titrimetric method are given in Table-I. It is evident from Table-II that the values of mean percent drug (theophylline) estimated by Indian Pharmacopoeial and proposed titrimetric methods are 96.08, and 99.08, respectively. The results of analysis by the proposed titrimetric method are comparable to the results obtained from the Indian Pharmacopoeial method. The amounts of drug estimated by Indian Pharmacopoeial and proposed titrimetric methods are very close to each other and very near to 100.0, indicating the accuracy of the proposed method of analysis.This indicates the accuracy of the proposed method. Low values of standard deviation, percent coefficient of variation and standard error (Table-II), further validated the proposed titrimetric method.

Table 1: Analysis data of theophylline bulk sample

S. no.	Amount of drug analyzed (mg)	Amount of drug found (mg)		Percent drug estimated	
		I.P.M	P.T.M	I.P.M	P.T.M
I	300	283.11	297.27	94.37	99.09
II	300	295.98	292.76	98.66	97.58
III	300	288.26	301.77	96.08	100.59
IV	300	285.68	297.27	95.22	99.09

P.T.M. = Proposed titrimetric method
I.P.M. = Indian Pharmacopoeial method.

Table 2: Statistical evaluation of analysis of theophylline bulk sample

Sno.	Method of Analysis	Percent Drug Estimated	Coefficient of Variation (mean + SD)	Standard Error (%)
I	I.P.M	96.08±1.854	1.854	0.927
II	P.T.M	99.0875±1.228	1.228	0.614

CONCLUSION

Hence, it can be concluded that the proposed method is new, simple, cost effective, accurate, safe and precise and can be successfully employed in the routine analysis of theophylline in bulk 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 proposed method is worth adopting in the respective Pharmacopoeia.

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