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DEVELOPMENT OF TITRIMETRIC METHOD FOR ESTIMATION OF FUROSEMIDE TABLETS BY USING MIXED CO-SOLVENCY PROCESS

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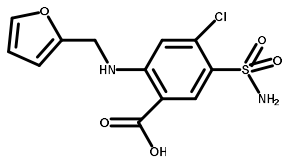
ABSTRACT

Titrimetric method for determination of furosemide in bulk drug and formulation is described here. In this method, solution of furosemide using different inorganic solvents were titrated against alkaline solution of sodium hydroxide using bromothymol blue as an indicator by mixed co-solvency process. The method was validated and the statistical evaluation of method was performed by inter-day and intraday precision. The accuracy and reliability of the proposed method was ascertained by comparison with a reference method. This method is beneficial over the reported methods for estimation of furosemide tablets in such a way that here we are using inorganic solvents in place of organic solvents and thus the toxicity of solvents is decreasing. Inorganic solvents are cheap as compare to organic solvents that's why the method is cost effective.

Keywords: "Furosemide", "Mixed co-solvency process", "Titrimetric analysis", "Validation Parameters"

1. INTRODUCTION

Furosemide consists an anthranilic acid nucleus as parent nucleus in its structure **[1]**. It is a diuretic **[2]** used in the treatment of hypertension **[3]**, edema associated with pulmonary **[4]**, hepatic **[5]** and renal **[6]** disease. Furosemide act on loop of Henle and hence it comes in category of loop diuretic **[7]** and high celling diuretic **[8]**.



4-chloro-2-((furan-2-ylmethyl)amino)-5-sulfamoylbenzoic acid

Several methods are reported for estimation of furosemide in pharmaceutical dosage forms. From that, some methods are chromatographic methods like high performance liquid chromatography (HPLC) **[9]-[14]**, liquid chromatography – mass spectrometry (LC-MS) **[15]**, micellar liquid chromatography (MLC) **[16]**, thin layer chromatography(TLC) **[17]**. Few other methods are also reported like differential pulse voltammetry (DPV) **[18]**, proton nuclear magnetic resonance spectroscopy (H^1NMR) **[19]** and UV-spectrophotometry **[20]** have been applied for assay of furosemide in bulk drug as well as formulations.

Several titrimetric methods are also reported for determination of furosemide but these all are dependent on organic solvents for dissolution of furosemide. Organic solvents are harmful to human beings and also costly. Here, we have developed a titrimetric method using inorganic solvents by mixed co-solvency process which is cheap method and inorganic solvents are not as harmful to human being as organic solvents.

Mixed hydrotropic concept describes the increase in solubility of a solute by increasing concentration of alkali metal salts of organic acids **[21]**. The hydrotropic solubilization process consist of intermolecular interaction with several molecular forces rather than either a specific complexation event or a process dominated by a medium effect, such as co-solvency or saltingin **[22]**. Hydrotropic agents have been observed to enhance the aqueous solubility of poorly water-soluble drugs **[23]**. Aim of our work is to increase solubility of furosemide in bland of inorganic solvents rather than organic solvents by using mixed hydrotropic concept.

2. METHODS AND MATERIALS

2.1 Reagents and chemicals

All chemicals used were of analytical grade and solutions were prepared using double distilled water. Furosemide was received from Zydus as a gift sample. Various inorganic reagents as titrant like urea, sodium acetate, sodium citrate, sodium benzoate and phosphate bufferof different pH were used as solvent in mixed co-solvency process to dissolve furosemide. Sodium hydroxide was used as titrant and bromothymol blue as an indicator.

2.2 Apparatus

Apparatus for titrimetric analysis is an assemble of burette and volumetric flask. Otherglass wares used were beaker, pipettes etc.

2.3 Procedure

2.3.1 Procedure for API

500mg of furosemide was accurately weighed and dissolved in 100 ml bland consisting of phosphate buffer [pH 7], 1M sodium acetate and 0.4M sodium citrate and titrated with 0.1M sodium hydroxide using bromothymol blue as an indicator. Blank titration was performed using 100ml of bland of mixed hydrotropic solution.

2.3.2 Procedure for tablet

Twenty tablets were accurately weighed and ground into a fine powder with mortar and pestle and amount of powdered placed into 250ml of volumetric flask. In a flask 100ml of bland consisting of phosphate buffer [pH 7] 1M sodium acetate 0.4M sodium citrate was added. The flask was shaken for about 5 min to solubilize the drug and titrated with 0.1M sodium hydroxide using bromothymol blue as an indicator. Blank titration was performed using 100ml of blend using mixed hydrotropic solution.

3. RESULT AND DISCUSSION

The % purity of furosemide as API was found to be 103% by using mixed hydrotropic concept and the % purity of furosemide tablet was found to be 105 % by using mixed hydrotropic concept. We have used various hydrotropic blends as titrant that are given in the below **Table 1**. % Purity was calculated by using the following equation:

Each ml of 0.1M NaOH is equivalent to 0.03307 gm of furosemide.

3.1 Validation Parameters

3.1.1 Accuracy and Precision

To determine accuracy and precision of the present method, pure furosemide at three different levels was determined and it was performed seven times. **Table 2** summarizes the relative error (%) and relative standard deviation which reveal the high accuracy and precision of the proposed method. Reproducibility of the method was performed for the standard drug solution at three levels each day for five days. The day-to-day results of RSD values were in the range of 1.85 to 2.35 % which represents the best use of the method in routine laboratory use.

3.1.2 Determination of Furosemide in tablets

Titrimetric analysis using mixed co-solvency concept was applied to some representative furosemide tablets commercially available in the market. The drug concentration in same batch tablets was determined by the present method and the results are described in the **Table 3**. The results were compared between the proposed method and the reference method and they were close to each other.

Statistical methods are also applied for comparison of results. For accuracy, Student's t test and for precision, variance ratio F-test was performed at 95% confidence level. The results in **Table 3**

indicates that there is no significant difference between the proposed and reference methods in terms of accuracy and precision.

Recovery study was performed to prove validity and accuracy of the novel method. Tablet powder with known concentration was spiked with standard furosemide powder at three different levels and the total concentration was found by the novel method. Each determination was performed three times. The recovery study is described in **Table 4**.

Table 1: Trial of various solvent ratios

Sr no.	Trial	Titrate [NaOH]	Titrant	%Purity [%w/v]
1	1	1	1M phosphate buffer 1M sodium acetate 1M sodium citrate	218
2	2	1	2M phosphate buffer 1M sodium acetate 0.5M sodium citrate	118
3	3	2	1M phosphate buffer 0.5M sodium acetate 1M sodium citrate	362
4	4	1	4M phosphate buffer 1M sodium acetate 0.4M sodium citrate	208
5	5	0.5	5M phosphate buffer 0.5M sodium acetate 0.4M sodium citrate	104
6	6	0.1	5M phosphate buffer 1M sodium acetate 0.4M sodium citrate	100
Lasix tablet	-	0.1	5M phosphate buffer 1M sodium acetate 0.4M sodium citrate	105
Frusenex tablet	-	0.1	5M phosphate buffer 1M sodium acetate 0.4M sodium citrate	103
Salinex tablet	-	0.1	5M phosphate buffer 1M sodium acetate 0.4M sodium citrate	104

Table 2: Evaluation of accuracy and precision of method

Drug taken, mg	Drug found, mg	RE %	RSD %	Range of error, %
5.0	5.08	1.60	1.87	± 1.80
10.0	9.92	0.80	0.36	± 0.35
15.0	14.72	1.87	0.55	± 0.53

Table 3: Results of assay of formulations

*Brand name of furosemide tablet	Label claim, mg/tablet	**Found (label claim ± SD)	
		Reference Method	Titrimetry Method
Frusenex[a] tablet	40	101.36 ± 0.58	100.96 ± 1.46 t = 1.28 F = 3.21
Lasix[b] tablet	40	102.66 ± 0.74	101.42 ± 1.84 t = 3.12 F = 6.98
Salinex[c] tablet	40	103.66 ± 0.82	105.28 ± 1.64 t = 3.50 F = 4
*Marketed by: a. Geno Pharmaceuticals ltd; b. Hoechst Morrison Roussel ltd; c. Indian Drugs and Pharmaceuticals ltd.			

Table 4: Results of Recovery Study by Standard Addition Technique.

Formulation studied	Amount in formulation, mg	Pure drug added, mg	Total found, mg	Recovery of pure drug added, %
Frusenex Tablet	3.03 3.03 3.03	5.0 10.0 15.0	8.16 13.35 18.24	102.64 103.18 101.39
Lasix Tablet	3.06 3.06 3.06	5.0 10.0 15.0	8.08 13.23 18.66	100.38 101.66 104.03
Salinex Tablet	3.0 3.0 3.0	5.0 10.0 15.0	7.93 12.79 18.04	98.62 97.88 100.24

4. CONCLUSION

The titrimetric analysis of furosemide as pure drug as well as in tablets was performed by using mixed co-solvency concept. Reported methods have used organic solvents to dissolve furosemide but these organic solvents are harmful to human being and also are very costly therefore to minimize these drawbacks we have used inorganic solvents here. Furosemide in inorganic solvent is very slightly soluble or insoluble therefore we have used mixed co-solvency concept and used three different solvents in three different ratios. From results and validation parameters, the proposed method is valid for determination of furosemide in bulk drug as well as furosemide tablets.

5. CONFLICT OF INTEREST: Authors declare no conflict of interest.

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