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A NOVEL AND VALIDATED ECOFRIENDLY TITRIMETRIC METHOD FOR THE ESTIMATION OF FRUSEMIDE IN SOLID DOSAGE FORMS

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ABSTRACT

Background: Frusemide, a widely used loop diuretic, exhibits poor water solubility, which poses a challenge for its quantitative estimation using conventional aqueous titrimetric methods. Standard procedures often involve toxic organic solvents like dimethylformamide (DMF), raising environmental and safety concerns. **Objective:** The objective of this study was to develop a simple, accurate, and ecofriendly titrimetric method for the estimation of Frusemide in tablet formulations by employing a hydrotropic solubilization technique. **Methodology:** Aqueous solubility of Frusemide was enhanced using 50% urea solution, enabling its titrimetric estimation without the use of organic solvents. The method involved titrating Frusemide with 0.1 M sodium hydroxide using bromothymol blue as an indicator. Commercial tablet formulations were analyzed using this approach and compared with the standard method prescribed in the Indian Pharmacopoeia (IP). Recovery studies were conducted to validate the accuracy of the method. **Results:** The proposed method demonstrated effective solubilization of Frusemide and produced sharp titration endpoints. The percentage of drug content found in tablet formulations ranged from 96.1% to 96.7%, which was comparable to values obtained using the IP method. Recovery rates were close to 100%, and the method showed excellent precision with low relative standard deviations (<2%). No interference from excipients or the hydrotropic agent was observed. **Conclusion:** The developed method is a reliable, reproducible, and environmentally friendly alternative for the routine analysis of Frusemide in solid dosage forms. By eliminating hazardous organic solvents, it aligns with green chemistry principles and is especially suited for resource-limited laboratory settings.

KEYWORDS: Frusemide, Hydrotropy, Titrimetric Analysis, Urea, Ecofriendly Method, Green Chemistry.

1. INTRODUCTION

Frusemide, a powerful loop diuretic, is commonly prescribed for treating conditions such as edema and hypertension. Ensuring the precise quantification of Frusemide in pharmaceutical products is essential for maintaining its therapeutic effectiveness and safety profile.[1-2] Despite this, many conventional analytical techniques used for its estimation rely on hazardous organic solvents, raising concerns regarding environmental and occupational safety. Chemically identified as 5-(aminosulfonyl)-4-chloro-2-[(2-furanylmethyl) amino] benzoic acid, Frusemide is commercially available under various brand names, including Lasix, Frucix, and Frusemide itself. It has the molecular formula $C_{12}H_{11}N_2O_5S$ and a molecular weight of 330.77 g/mol. The compound appears as a white to pale yellow crystalline powder, characterized by a faint odor and minimal taste. While its solubility in water, chloroform, and ether is limited, it dissolves well in solvents such as acetone and methanol.[3-4]

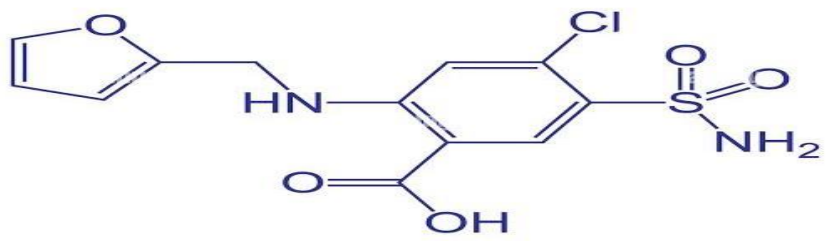

Figure 1: Furosemide Chemical Structure.

As a commonly prescribed medication, the accurate determination of Frusemide in pharmaceutical formulations is crucial to ensure its efficacy and safety. The presence of impurities or degradants in Frusemide formulations can significantly affect its therapeutic efficacy and toxicity profile.

Titrimetry is a simple, cost-effective analytical technique often applied in pharmaceutical analysis. However, its use for Frusemide is limited by the drug's poor aqueous solubility. To overcome this, hydrotropic agents are employed to enhance drug solubility, facilitating titrimetric analysis without organic solvents.[5]

Hydrotropes are class of chemical substance which cause a several fold increase stability of a water insoluble solute under normal conditions. Neuberg in 1916 identified this pioneering technique for solubility enhancements for a variety of sparingly soluble organic solutes. Hydrotropes are water-soluble, surface-active compounds that significantly enhance the aqueous solubility of poorly soluble organic compounds through complex formation. Common hydrotropes include sodium benzoate, sodium salicylate, nicotinamide, and urea. and urea is the most popular examples of hydrotropic agents that have been used for solubilization of poorly water soluble drugs for their analysis.[6-7]

Advantages of avoiding organic solvents[8]

- Reduced cost
- Minimized toxicity
- Decreased environmental impact
- Enhanced safety and reproducibility

This study investigates the use of 50% urea solution to enhance the solubility of Frusemide, allowing ecofriendly titrimetric analysis of its solid dosage forms.[9-10]

2. MATERIALS AND METHODS

All chemicals and solvents used were of analytical grade, Electronic balance, and Frusemide tablets were purchased from local market. Reference standard of Frusemide obtained from Indian pharmacopoeia commission Ghaziabad.

2.2 Apparatus

- Electronic analytical balance
- Standard titration setup
- Glassware as per analytical requirement

2. Experimental

3.1 Preliminary Solubility Studies

Solubility of Frusemide was tested in varying concentrations of urea solutions (10%, 20%, 30%, 40%, and 50%) at 28 ± 1°C. Excess drug was added to each solution and titrated after filtration. Blank corrections were made. Maximum solubility was observed in 50% urea solution, which was selected for further study.

3.2 Estimation of Frusemide Bulk Drug (IP 1996 Method)[16]

- 500 mg of bulk Frusemide was dissolved in 40 mL of DMF.
- Titrated with 0.1 M NaOH using bromothymol blue as indicator.
- Blank titration was performed.
- Each mL of 0.1 M NaOH is equivalent to 0.03307 g of Frusemide.

3.3 Estimation of Frusemide Tablets (Proposed Method)

- Twenty tablets (Formulations I & II) were weighed, powdered, and an amount equivalent to 500 mg Frusemide was taken.
- Dissolved in 40 mL of 50% urea solution.
- Titrated with 0.1 M NaOH using bromothymol blue (color change from pale yellow to persistent blue).
- Drug content was calculated and results are shown in Table. 1

4. Recovery Studies

To assess the accuracy and reproducibility, recovery studies were conducted. Known quantities of standard Frusemide (10 mg and 25 mg) were spiked into pre-analyzed tablet powder equivalent to 500 mg Frusemide. The recovery was determined by the proposed method and compared with the IP method.

5. RESULTS AND DISCUSSION

This study presents a newly developed titrimetric method for estimating Frusemide in tablet dosage forms using a hydrotropic approach. Urea, a safe and cost-effective compound, was used to enhance the aqueous solubility of Frusemide, a drug known for its poor solubility in water. This method eliminates the need for harmful organic solvents and offers an environmentally sustainable analytical alternative.

5.1 Solubility Enhancement

Preliminary Solubility studies conducted at different concentrations of urea revealed a remarkable increase in Frusemide solubility with increasing urea concentration. Among the tested solutions, 50% urea demonstrated the highest solubilizing effect. Compared to distilled water, solubility increased approximately tenfold, enabling smooth titrimetric analysis. The drug dissolved completely in 50% urea, resulting in a clear solution suitable for titration. No precipitation or degradation was observed during the analysis, indicating that the hydrotropic agent did not interfere with the drug's chemical integrity or the titration reaction.

The choice of urea is justified by its well-established hydrotropic properties, which are believed to enhance solubility through weak interactions such as hydrogen bonding or stacking between the drug and hydrotropic molecules. This approach avoids the use of volatile organic compounds and supports sustainable analytical practices.

Table 1: Analysis Data of Frusemide Tablet Formulations.

Tablet Formulation	Label claim	% drug estimated	Coefficient of Variation
I	40 mg	96.7%	0.994
II	40 mg	96.3%	0.991

5.2 Method Performance and Comparison with IP Method

The proposed titrimetric method was successfully applied to two commercially available Frusemide tablet formulations, each labelled to contain 40 mg of the drug. The results showed a consistent and accurate estimation of drug content, with measured values ranging from 96.1% to 96.7%. These values closely matched those obtained using the Indian Pharmacopoeia (IP) method, which ranged from 95.2% to 95.4%, indicating that the new method is both comparable and reliable. The coefficient of variation was below 1%, indicating excellent repeatability and precision.

The sharp endpoint observed during titration, indicated by a clear color change with bromothymol blue, confirmed the suitability of this method for accurate quantification. The consistency across samples suggests that tablet excipients did not interfere with the determination process, affirming the method's specificity.

Table 2: Comparative Recovery Data of Frusemide by Proposed Indian Pharmacopeia method.

Formulation	Label claim	Eq wt of Drug taken	Amount found		% estimated	
			Proposed method	IP method	Proposed Method	IP method
I	40mg	500mg	38.4 mg	38.2 mg	96.1	95.4
II	40mg	500mg	38.9 mg	38.1 mg	96.3	95.2

5.3 Accuracy and Precision: Recovery Studies

To further confirm the accuracy of the developed method, recovery experiments were performed by adding known amounts of pure Frusemide to pre-analyzed tablet powder. The recovery rates for both formulations were very close to 100%, with minimal deviation. These findings indicate that the method can accurately measure the active pharmaceutical ingredient

even when present with common excipients. The relative standard deviations (RSD) were well below 2%, signifying excellent precision and repeatability.

5.4 Validation Highlights

Following the ICH guidelines, the method was validated for key performance characteristics:

- Accuracy: Recovery data showed excellent agreement between expected and observed values, confirming that the method accurately estimates drug content without interference.
- Precision: Low RSD values from multiple replicate estimations showed that the method produces consistent results under the same conditions.
- Specificity: The method selectively determined Frusemide without interference from excipients or the hydrotropic agent. This was evident from the clean and consistent titration endpoint.
- Robustness and Simplicity: The method demonstrated resilience to small changes in procedure, such as minor variations in reagent volume, making it robust and easy to perform.

5.5 Environmental and Practical Considerations

A key advantage of the proposed method is its alignment with green chemistry principles. By replacing toxic organic solvents with 50% urea solution, this method reduces environmental hazards, improves workplace safety, and lowers analytical costs. Urea is inexpensive, non-toxic, and easily handled, making the method especially suitable for routine use in pharmaceutical quality control laboratories, particularly in settings with limited resources.

6. CONCLUSION

The study presents a novel, simple, ecofriendly, and validated titrimetric method for estimating Frusemide in tablet formulations. The method avoids harmful organic solvents by employing hydrotropic solubilization with 50% urea. It offers accurate, precise, and reproducible results suitable for routine quality control of Frusemide-containing pharmaceuticals.

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