Novel Spectrophotometric Estimation of Frusemide Using Hydro tropic Solubilization Phenomenon

R. K. MAHESHWARI*, S. DESWAL, D. TIWARI, N. ALI, B. POTHEN AND S. JAIN
Department of Pharmacy, S. G. S. I. T. S, 23, Park Road, Indore - 452003, India

*For correspondence
E-mail: rkrkmaheshwari@yahoo.co.in

Maheshwari, et al.: Spectrophotometric Estimation of Frusemide

A novel, safe and sensitive method of spectrophotometric estimation in ultraviolet region has been developed using 0.5 M ibuprofen sodium solution as hydrotropic solubilizing agent for the quantitative determination of frusemide, a poorly water-soluble diuretic drug in tablet dosage form. Frusemide shows maximum absorbance at 330 nm. Beer's law was obeyed in the concentration range of 20 to 100 µg/ml. Ibuprofen sodium does not absorb above 300 nm. Commonly used tablet excipients and ibuprofen sodium did not interfere in spectrophotometric estimation. Results of the analysis were validated statistically and by recovery studies. Using 0.5 M ibuprofen sodium solution for analysis of two different tablet formulations of frusemide, the percent label claims and percent recoveries estimated were close to 100 with low values of standard deviation, percent coefficient of variation and standard error.

Key words: Frusemide, hydro tropy, ibuprofen sodium, spectrophotometry

Increasing the aqueous solubility of insoluble and slightly soluble drugs is of major importance. Various techniques have been employed to enhance the aqueous solubility of poorly water-soluble drugs. Hydro tropic solubilization is one of them. The term hydro tropy has been used to designate the increase in solubility in water of various substances due to the presence of large amounts of additives. Sodium salicylate, sodium benzoate, urea, nicotinamide, sodium citrate and sodium acetate are the most common examples of hydro tropic agents1-15. Maheshwari has analyzed various poorly water-soluble drugs using hydro tropic solubilization phenomenon viz. ketoprofen1, frusemide4, cefixime5, salicylic acid4, tinidazole6 and amoxycillin7. Maheshwari et al, have developed various analytical techniques employing hydro tropic solubilisation phenomenon to analyze poorly water-soluble drugs like hyrochlorothiazide8, aceclofenac8 and ofloxacin10.

Various organic solvents such as methanol, chloroform and dimethyl formamide, have been employed for solubilization of poorly water-soluble drugs to carry out spectrophotometric analysis. Drawbacks of organic solvents include their higher cost, toxicity and pollution. Hydro tropic solution may be a proper choice to preclude the use of organic solvents.

Frusemide (4-chloro-N-furfuryl-5-sulphamoylanthranilic acid) is a widely used diuretic drug. In the preliminary solubility studies there was more than 105 fold enhancement in the solubility of frusemide in 0.5 M ibuprofen sodium solution. Therefore, it was thought worthwhile to employ this hydro tropic solution to extract out the drug from fine powder of tablets to carry out spectrophotometric estimation.

There is broad scope for hydro tropic agents in quantitative estimations of other poorly water-soluble drugs. Shimadzu UV/Vis recording spectrophotometer (Model UV160A) with 1 cm matched silica cell was employed. Frusemide was obtained from M/s Alkem Lab Ltd, Mumbai. All other chemicals were of analytical grade.

For the preparation of 0.5 M ibuprofen sodium solution, 10 g of sodium hydroxide was dissolved in 200 ml of distilled water. Ibuprofen (51.6 g) was added little at a time and stirred to dissolve. After complete addition of ibuprofen, the pH was adjusted to remain between 7.5 to 8.0 with sodium hydroxide to assure the complete neutralization of ibuprofen. Then the volume was made up to 250 ml with distilled water.

For the preparation of a calibration curve, 100 mg of the drug was dissolved in 10 ml of 0.5 M ibuprofen sodium solution and diluted up to 100 ml with distilled water. The standard solution (1000 µg/ml) was further diluted with distilled water to obtain
20, 40, 60, 80 and 100 µg/ml. Absorbances were noted against respective reagent blanks to plot the calibration curve.

In the preliminary solubility studies the solubility of frusemide was determined in distilled water and 0.5 M ibuprofen sodium solution at 27±1°C. Enhancement in the solubility of frusemide in 0.5 M ibuprofen sodium solution was more than 105 folds (as compared to its solubility in distilled water).

Analysis of tablet formulation of frusemide by the proposed method was done by a method in which two different marketed tablet formulations of frusemide were used. Twenty tablets of frusemide from formulation 1 (Lasix, Aventis Pharma Limited, Ankleshwar) were weighed and ground to a fine powder. An accurately weighed powder sample equivalent to 100 mg of frusemide was transferred to a 100.0 ml of volumetric flask containing 10 ml of 0.5 M ibuprofen sodium solution. The flask was shaken for about 5 min to solubilize the drug and the volume was made up to mark with distilled water. The solution was filtered through Whatmann filter paper No 41. The filtrate was diluted appropriately with distilled water and was analyzed on UV spectrophotometer against reagent blank. Drug content of tablet formulation was then calculated (Table 1). Tablet formulation 2 (Frusenex-100, Geno Pharmaceuticals Limited, Goa) was treated in the same way.

Recovery studies were performed adding pure drug in the preanalysed tablet powder and following the same method of analysis. All types of analysis were performed in triplicate. Percent label claims estimated by the proposed method were 99.08±2.016 and 98.73±0.458 (Table 2), which were near to 100, indicating the accuracy of the proposed method. Low values of standard deviation, percent coefficient of variation and standard error further validated the proposed method. Percent recoveries ranged from 97.58±1.008 to 99.30±0.922 (Table 3). All these values were very close to 100. Also the values of standard deviation, percent coefficient of variation and standard error were satisfactorily low. This further confirmed the accuracy, reproducibility and validity of the proposed method.

ACKNOWLEDGEMENTS

Authors are grateful to M/s. Alkem Lab. Ltd., Mumbai for providing the gift sample of drug.

REFERENCES

4. Maheshwari RK. Analysis of frusemide by application of hydrotropic

---

**TABLE 1: RESULTS OF ANALYSIS OF FRUSEMIDE TABLET FORMULATIONS**

<table>
<thead>
<tr>
<th>Amount of drug in tablet powder</th>
<th>Amount found (mg)</th>
<th>Percentage estimated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Formulation 1</td>
<td>Formulation 2</td>
</tr>
<tr>
<td>100</td>
<td>97.36</td>
<td>99.11</td>
</tr>
<tr>
<td>100</td>
<td>98.59</td>
<td>98.86</td>
</tr>
<tr>
<td>100</td>
<td>101.30</td>
<td>98.22</td>
</tr>
</tbody>
</table>

Formulation 1 is Lasix, Aventis Pharma Limited, Ankleshwar and Formulation 2 is Frusenex-100 of Geno Pharmaceuticals Limited, Goa.

**TABLE 2: STATISTICAL EVALUATION OF ANALYSIS OF TABLETS**

<table>
<thead>
<tr>
<th>Tablet formulation</th>
<th>Mean % estimation</th>
<th>Standard deviation</th>
<th>% coefficient of variation</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>99.08</td>
<td>2.016</td>
<td>2.035</td>
<td>1.164</td>
</tr>
<tr>
<td>2</td>
<td>98.73</td>
<td>0.458</td>
<td>0.464</td>
<td>0.264</td>
</tr>
</tbody>
</table>

Formulation 1 is Lasix, Aventis Pharma Limited, Ankleshwar and Formulation 2 is Frusenex-100 of Geno Pharmaceuticals Limited, Goa.

**TABLE 3: RESULTS OF RECOVERY STUDIES OF TABLET FORMULATION WITH STATISTICAL EVALUATION**

<table>
<thead>
<tr>
<th>Tablet formulation</th>
<th>Drug present in preanalysed tablet powder (mg)</th>
<th>Pure drug added (mg)</th>
<th>% recovery estimated* (mean±SD)</th>
<th>% coefficient of variance</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>20</td>
<td>98.33±1.231</td>
<td>1.252</td>
<td>0.711</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>40</td>
<td>98.76±0.813</td>
<td>0.823</td>
<td>0.469</td>
</tr>
</tbody>
</table>

*Formulation 1 is Lasix, Aventis Pharma Limited, Ankleshwar and Formulation 2 is Frusenex-100 of Geno Pharmaceuticals Limited, Goa.*

---


In Vivo Pharmacokinetic Studies of Prodrugs of Ibuprofen

ABHA DOSHI* AND S. G. DESHPANDE
C. U. Shah College of Pharmacy, S. N. D. T. Women’s University, Mumbai – 400 049, India

Doshi, et al.: Pharmacokinetics of Prodrugs of Ibuprofen

In vivo pharmacokinetic studies of N-Mannich base derivatives of ibuprofenamide as prodrugs were performed on rabbits. Ibuprofen and both the prodrugs (IBM B-M and IBM B-P) were administered orally and at different time intervals blood samples were collected and assayed for ibuprofen and ibuprofenamide by HPLC method. From the plasma concentration-time profile; \( C_{(peak)} \), \( t_{(peak)} \), AUC and the time required to achieve minimum effective concentration were calculated. N-Mannich base prodrugs first get hydrolyzed to ibuprofenamide which in turn gets hydrolyzed to ibuprofen by the enzyme amidase. The \( (C_{(peak)}) \) and AUC values of IBM B-M were found to be more compared to IBM B-P. In both the cases ibuprofen started appearing after 2 h and it required minimum 4 h to get the ibuprofen in therapeutic range. Both the prodrugs released ibuprofen slowly which gave sustained effect. IBM B-M provided ibuprofen in therapeutic range for 48 h and IBM B-P for 24 h.

The non-steroidal antiinflammatory agents have major drawbacks of causing gastrointestinal ulcerogenicity. The prodrug approach was used to get a safer NSAID, where the drug containing –COOH or –OH group is converted to prodrug. The prodrugs of ibuprofen were prepared as N-Mannich base derivatives of ibuprofenamide using either morpholine or piperidine as amine component. Two prodrugs of ibuprofen were synthesized. These were, N-(morpholinomethyl) ibuprofenamide hydrochloride (IBMB-M) and N-(piperidinomethyl) ibuprofenamide hydrochloride (IBMB-P)\(^1\). The in vitro kinetic studies of the prodrugs were performed in aqueous buffers at different pH values in simulated gastric and intestinal fluids and in human plasma at 37°. The results showed that hydrolysis took place in two steps. First the N-Mannich base was hydrolyzed to ibuprofenamide which was pH-dependent and then ibuprofenamide was converted to ibuprofen which was enzymatically controlled\(^2\).

The prodrug behaves differently under in vitro and in vivo conditions because many biological factors play an important role in bioavailability and release rate of drug from prodrug during in vivo studies. The ideal way to observe the appearance of drug from prodrug is by actual studies in humans. But as the prodrugs are new drugs, it is not feasible to perform in vivo studies directly on humans\(^3\). Rabbit was selected

*For correspondence
E-mail: abha_doshi@yahoo.com
MET’s Institute of Pharmacy,
Bandra Reclamation, Bandra (w), Mumbai-400 050, India