ASSAY OF NIMESULIDE BY
ION ASSOCIATION TITRATION

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Abstract
The present paper presents a new two-phase titrimetric method for the assay of
nimesulide. The method is based on the solvent extraction of nimesulide using
tetradecyltrimethylammonium bromide (cetrimide) as ion association reagent. Thymol blue
was used as indicator. The proposed method was successfully applied to the nimesulide
assay in bulk and pharmaceutical dosage forms.

Keywords: ion association; titrimetry; nimesulide

Introduction
The capacity of different pharmaceutical substances to form ionic
associations was used to develop gravimetric, titrimetric, electrometric,
spectrometric and chromatographic methods for their assay in bulk and
pharmaceutical dosage forms.

The characteristic of the ion association titration methods consist in
the use of a two-phase (water – organic solvent) system. The end point
detection is based on the different stabilities of the ion pairs formed between
the determined substance with the titrant and with the indicator [1].

The two-phase ion-pair titration was applied to the determination of
some basic pharmaceutical substances such as timolol [2], cilazapril [2],
bromhexine [2], cinnarizine [3], dipyridamole [3], local anesthetics
(procaine, dibucaine, tetracaine)[4].

Nimesulide, 4 - nitro - 2 - phenoxy - methanesulfonanilide (figure
1) is a non-steroidal anti-inflammatory drug with antipyretic and analgesic
properties [5].
Figure 1
Chemical structure of nimesulide

The published methods reporting the determination of nimesulide in pharmaceutical formulations are based on various techniques: fluorimetry [6], spectrophotometry [7-11], HPLC [12 - 14], thin layer chromatography [15], voltametry [16] and capillary electrophoresis [17].

This paper presents a new ion association titration method for the assay of nimesulide. The proposed method is simple and suitable for routine determination. The method also provides economic procedures and is less time consuming compared with the spectrophotometric and HPLC methods.

Materials and methods

Material and reagents

All chemicals and reagents were of analytical grade. Whenever we refer to water it was used distilled water.

- Nimesulide was supplied by Magistra S.A. Substance purity was checked by determination of the melting point (149°C) and the registration of IR spectrum; the content was determined by potentiometric titration using the official method (European Pharmacopoeia 6.0) (100.14±0.55, n=6);
- Tetradecyltrimethylammonium bromide (Acros Organics);
- Thymol blue (Merck);
- Nimesulide solution was prepared by dissolving 0.1017 g substance into 100 mL chloroform;
- Tetradecyltrimethylammonium bromide (cetrimide) standard solution, 4·10⁻³M was prepared by dissolving 1.3517 g cetrimide into 1000 mL of distilled water. The cetrimide standardization was based on Pifer-Wollish method;
- Thymol blue solution was prepared by dissolving 0.1051 g substance in 5 mL NaOH 10⁻¹M. The solution obtained was completed to 100 mL with distilled water;
- NaOH 10⁻¹M solution was prepared by diluting the appropriate volumes of 1M solution;
- Chloroform was used without previous purification.
Methods

Procedure

Volumes of 10 mL nimesulide solution, 15 mL chloroform, 15 mL distilled water, 1 mL thymol blue solution and 1 mL NaOH 10^{-1}M solution are transferred in a 200 mL conical flask. The mixture was shaken vigorously and titrated with \(4 \times 10^{-3}\)M cetrimide solution. When the end point is reached the color of the organic phase turns from yellow to green.

Procedure for the assay of dosage forms

Tablets

20 tablets (Aulin® - 100 mg nimesulide per tablet – CSC Pharmaceuticals) were weighed, grounded into a fine powder and mixed. An accurately weighed portion of the powder equivalent to one tablet was transferred into a 100 mL volumetric flask. 25 mL of chloroform were added and after 20 min of mechanically shaking, the suspension was completed to the mark with the same solvent. Volumes of 10mL of the suspension obtained were titrated using the procedure described in the previous paragraph.

Granules

The content of 10 sachets of granules for oral suspension (Aulin® - 100 mg nimesulide per sachet – CSC Pharmaceuticals) were weighed, ground into a fine powder and mixed. An accurately weighed portion of the powder equivalent to one sachet was transferred into a 100 mL volumetric flask. 25 mL of chloroform were added and after 20 min of mechanically shaking, the suspension was completed to the mark with the same solvent. Volumes of 10mL of the suspension obtained were titrated using the procedure described previously.

Results and discussion

Nimesulide is an acidic drug. It contains a sulphoanilide moiety which gives a weakly acidic character, pKa \(\approx 6.5\) [18,19]. In basic media (pH = 9 ± 0.5) the ionization and deprotonation of sulphoanilide group occur and the anionic form of nimesulide can react with a positively charged ion to form an ionic association.

The capacity of nimesulide to form ionic association with different quaternary amonium ions such as hexadecyltrimetilammonium, hexadecylpyridinium and tetradecyltrimetilammonium was studied. Tetradecyltrimetilammonium has been found to be the optimum counterion. The ion-pair formed between nimesulide (NS) and cetrimide (CT) in basic media (NaOH), extractible in chloroform, has a yellow color and
maximum absorption at 410 nm. In the same experimental conditions thymol blue (TB) forms with the titrant an ion-pair colored in blue with maximum absorption at 613 nm.

The reaction before the equivalent point is:

$$\text{CT}^+ + \text{NS}^- \rightarrow \text{CT}^+ \cdot \text{NS}^-$$

After the equivalence point, a drop of standard solution added changes the color of organic phase to green. The reaction is:

$$\text{CT}^+ + \text{TB}^- \rightarrow \text{CT}^+ \cdot \text{TB}^-$$

The influence of the concentration of nimesulide on the detection of the end point has been studied. The results obtained show a good accuracy for the samples corresponding to 0.0110-0.0112 g nimesulide.

Using the proposed method nimesulide has been determined in bulk and pharmaceuticals dosage forms. The obtained results are presented in Table I.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Recovery* (%)</th>
<th>RSD (%)</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk</td>
<td>100.08</td>
<td>0.83</td>
<td>100.08 ± 0.64</td>
</tr>
<tr>
<td>Tablets</td>
<td>99.66</td>
<td>0.59</td>
<td>99.66 ± 0.45</td>
</tr>
<tr>
<td>Granules</td>
<td>99.87</td>
<td>0.49</td>
<td>99.87 ± 0.37</td>
</tr>
</tbody>
</table>

* Mean values of 9 determinations

**Conclusions**

The proposed method for the assay of nimesulide is simple, accurate, rapid, cheaper than an instrumental one and the procedures do not involve, even for the assay in pharmaceutical dosage forms, any critical reaction conditions or tedious sample preparation.

The developed method may be used for routine and quality control analysis of the investigated drug in dosage forms.

**References**

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