Fully automated sample preparation for the content determination of tablets

H. Risse

Metrohm — ion analysis

Summary

Benzbromaron is one of the main uricosuric drugs currently used. In addition to sophisticated and expensive LC-MS and GC-MS methods, benzbromaron can be effectively determined by titration with sodium hydroxide solution using a straightforward, fully automated sample preparation. A high-frequency homogenizer comminutes one or three tablets within 90 or 120 s, respectively. The overall analysis time is 8 minutes. Tenfold determinations with one or three tablets resulted in a benzbromaron content of 99.2 and 98.7 mg per tablet, respectively. Increasing the number of tablets from one to three lowers the RSD from 1.36 to 0.88%. These results show an excellent agreement with the benzbromaron amount indicated by the manufacturer (approx. 100 mg/tablet).

Besides the presented Titrando/homogenizer combination, the other two members of the 815 Robotic Soliprep Sample Processor family offer comprehensive sample preparation possibilities within the fields of IC, HPLC, ICP or voltammetry.

Introduction

The producing of pharmaceutical tablets requires proving that the active ingredient content given on the package is valid for each single tablet of a batch. Different analytical techniques such as titration or ion chromatography are used for the highly accurate quantitation of the ingredients. However, these analytical techniques are only as reliable as the sample preparation preceding them. Depending on the shape, coating, filling components used and concentration of the pharmaceutical ingredient, different sample preparation steps have to be carried out before the analysis proper.

The first step always is the thorough homogenization of the tablet in a suitable solvent mixture. Depending on the determination technique applied, steps such as additional dilution or pipetting are required. In most labs these steps are carried out manually, which can result in carryover or erratic results as the time-consuming and tedious manual operations are influenced by many different circumstances.

The above problems are solved by using an automated system that performs every sample preparation in exactly the same way. The content of the active ingredient in a single tablet as well as the product conformity of the whole batch can be determined with just one automation system. Automation not only improves reproducibility and accuracy, but also increases throughput as well as lab safety.

Instrumentation

	815 Robotic		
	Titration	Filtration	Flexible
Technique			Soliprep
Homogenization	●	●	●
Filtration/liquid handling	●	●	●
Sealed vials	●	●	●
Titration/direct measurement	●	●	●

The 815 Robotic Soliprep is a fully automated system designed for the preparation of sample solutions within the fields of ion chromatography, HPLC, ICP, voltammetry, titrimetric applications and more.

Sample preparation

- A defined number of tablets is directly weighed out into the sample vessel.
- After positioning the samples on the sample rack, all relevant analysis data such as weight, position and identification of the sample is entered into the sample data table of the *tiamo*™ software.
- Prior to comminution, the sample is transported to the second workstation where 60 mL methanol is added.
- Subsequently the Polytron comminutes the tablet for 90 s at 25'000 rpm; comminution of three tablets requires a comminution time of 120 s.
- 10 mL water is added to the homogenized sample.
- Using the 809 Titrando and the Solvotrode, benzbromaron is titrated with sodium hydroxide solution (1 mol/L).
- While the benzbromaron sample is being titrated, cleaning is performed fully automatically in the external rinsing station.
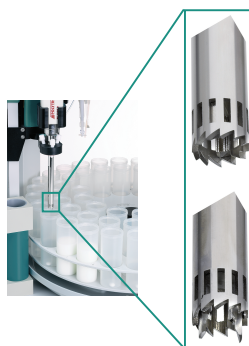
The high-frequency homogenizer aggregate with the protruding blade (154 mm) is used for sample particles larger than the diameter of the aggregate (12 mm).
The Polytron homogenizer is made by Kinematica AG, Switzerland.

Benzbromaron titration

Benzbromaron is a weak acid whose pKa (4.50) is comparable to that of acetic acid (4.75). After the loss of the hydrogen ion, the negative charge at the oxygen atom is delocalized around the ring (resonance stabilization). The more stable the ion is, the more likely it is to form. Hence, titration with strong bases is a convenient method for benzbromaron determination.
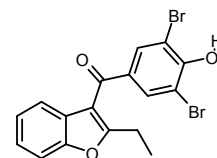
(3,5-dibromo-4-hydroxyphenyl)-2-ethyl-1-benzofuran-3-yl)methanon

Calculation

$$\text{Benzbromaron content [\%]} = \frac{EP1 \times M(NaOH) \times Titer \times MW(\text{benzbromaron})}{C00} \times 100$$

EP1: Titrant consumption up to end point in mL
M: Molarity of NaOH titrant in mol/L
Titer: Titer of the titrant used (dimensionless)
MW: Molecular weight of benzbromaron in g/mol (421.4 g/mol)
C00: sample size in mg

Determination with one tablet
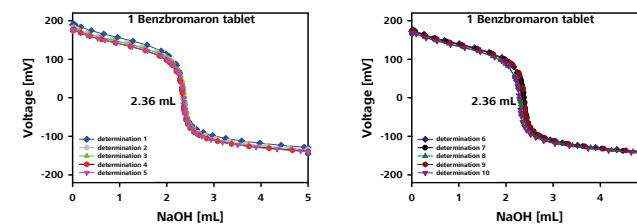
1 Benzbromaron tablet — 2.36 mL (determination 1–5)

1 Benzbromaron tablet — 2.36 mL (determination 6–10)

Determination no.	Sample weight [mg]	Titration EP1 [mL NaOH]	Benzbromaron Percentage [%]	Content [mg/tablet]
1	256.6	2.3523	38.53	98.9
2	256.6	2.3653	38.74	99.4
3	259.1	2.3630	38.65	100.2
4	255.1	2.3436	38.61	98.5
5	256.0	2.3763	39.01	99.9
6	258.4	2.3633	38.44	99.3
7	260.2	2.3971	38.72	100.7
8	260.6	2.3252	37.50	97.7
9	261.0	2.3936	38.54	100.6
10	249.5	2.2934	38.63	96.4
		Mean value		99.2
		RSD		1.36%

Determination with three tablets
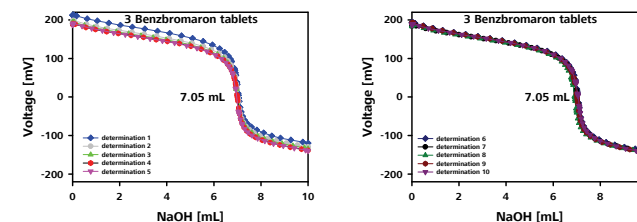
3 Benzbromaron tablets — 7.05 mL (determination 1–5)

3 Benzbromaron tablets — 7.05 mL (determination 6–10)

Determination no.	Sample weight [mg]	Titration EP1 [mL NaOH]	Benzbromaron Percentage [%]	Content [mg/tablet]
1	769.7	7.0266	38.37	98.4
2	771.2	6.9992	38.14	98.1
3	768.2	7.1721	39.24	100.5
4	768.0	7.0305	38.47	98.5
5	771.4	7.1075	38.72	99.6
6	774.3	7.0507	38.27	98.8
7	772.6	7.015	38.16	98.3
8	766.0	6.9506	38.14	97.4
9	773.5	7.0211	38.15	98.4
10	776.6	7.0817	38.32	99.2
		Mean value		98.7
		RSD		0.88%