Inline sample preparation – An effective tool for ion analysis in pharmaceutical products

N. Harihara Subramanian[1] and A. Wille[2]

Metrohm Ion analysis

Ion Chromatography

Summary

By means of azide analysis in Irbesartan a simple, fast, precise and accurate ion chromatographic method for the determination of traces of inorganic contaminants in pharmaceuticals is described. Traces of toxic azides in pharmaceutical products can accurately be determined in the sub-ppb range after Metrohm Inline Matrix Elimination using isocratic ion chromatography (IC) with suppressed conductivity detection. While the azide anions are retained on the preconcentration column, the interfering pharmaceutical matrix is washed away by a transfer solution, ideally consisting of 70% methanol and 30% ultrapure water. The analytical setup provides a well-resolved azide peak and thus alleviates the common drawback of excipient interferences, especially from the nitrate anion. Calibration with azide standards is linear over the range of 5…80 ppb, providing a coefficient of determination of 0.9995. The limit of detection (LOD) and the limit of quantitation (LOQ) of azide in Irbesartan are 5 and 30 µg/L, respectively; the relative standard deviations (RSD) for the peak area, peak height and retention time being smaller than 3.9%. Robustness testing involved variation of column oven temperature and composition of the transfer solution and, in terms of peak area, provided RSDs smaller than 2.8% and 3.1%, respectively.

Introduction

Alkali metal azides (MeN_3) are the key to the synthesis of a wide range of tetrazole derivatives such as Irbesartan, an antihypertensive pharmaceutical agent. When ingested or inhaled, azides or hydrazoic acid (HN_3) are highly toxic. Consequently, industries producing or using azide have to apply tight controls.

The most commonly applied analytical methods for determining the azide ion are spectrophotometry, capillary electrophoresis and gas chromatography (detection as HN_3). While the spectrophotometric method lacks sensitivity, the latter two methods suffer from labor-intensive derivatizations. The US Pharmacopeia suggests the use of direct-injection ion chromatography (IC). A transfer solution consisting of the IC eluent and suitable organic solvents removes the pharmaceutical from the analytical column. However, the procedure is tedious, time-consuming and cannot be automated.

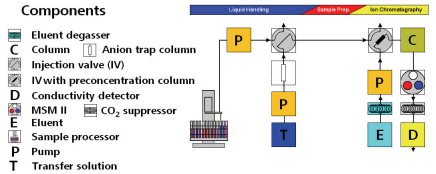
This poster presents a convenient ion chromatographic method using suppressed conductivity detection combined with previous matrix elimination that overcomes the mentioned drawbacks regarding sensitivity, selectivity and analysis time.

Instrumentation

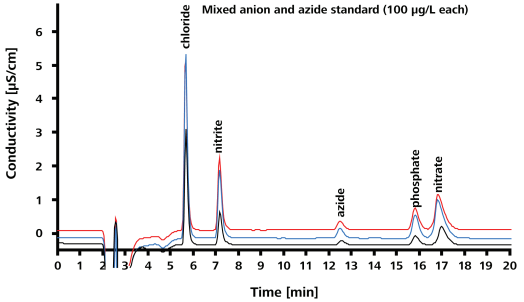
- Professional IC 850 Anion – MCS – Prep 2
- Professional Sample Processor 858 – Pump – Injector
- Metrosep A Trap 1
- Metrosep A PCC 1
- Metrosep A Supp 10 – 250
- Metrosep RP Guard

Matrix elimination

Ultratrace analysis of azides in pharmaceutical products is complicated by the presence of interfering Irbesartan ingredients. After the preconcentration of the azide on an anion preconcentration column and prior to chromatographic separation, Irbesartan ingredients are removed by rinsing the preconcentration column for 6 min with a transfer solution consisting of 70% methanol and 30% ultrapure water.



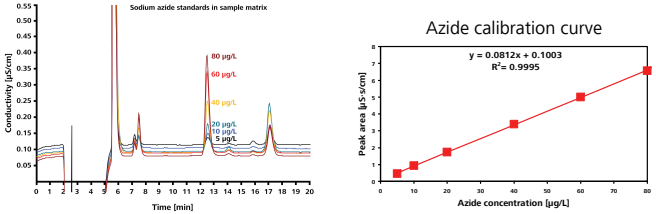
Separation performance



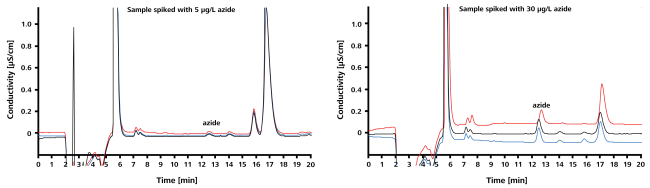
Column:	Metrosep A Supp 10 – 250	**Transfer solution:**	Methanol/water: 70/30
Column temp.:	60 °C	**Rinsing time:**	6 minutes
Eluent:	5 mmol/L sodium carbonate 5 mmol/L sodium hydrogen carbonate	**Flow:**	1.0 mL/min
		Loop:	1000 µL

The azide peak is well separated from those of the excipient anions. The indicated chromatographic conditions apply for all chromatograms shown.

Linearity

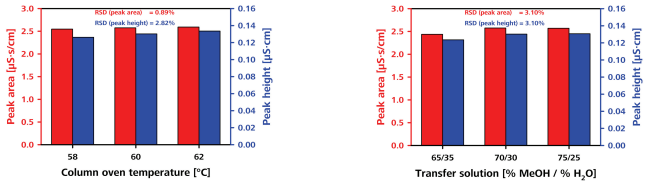


Precision and spike recoveries at LOD/LOQ



	5 µg/L spike				30 µg/L spike			
	Area [µS·s/cm]	Height [µS/cm]	RT [min]	Recovery [%]	Area [µS·s/cm]	Height [µS/cm]	RT [min]	Recovery [%]
1	0.41343	0.02094	12.5624	99.58	2.57938	0.12448	12.7078	103.26
2	0.42990	0.02070	12.5604	103.54	2.57259	0.13384	12.5214	103.33
3	0.42350	0.02076	12.5627	102.00	2.57423	0.13221	12.5228	103.54
Mean	0.42228	0.02080	12.5618	101.71	2.57540	0.13018	12.5840	103.38
SD	0.0083	0.0001	0.0013	1.9962	0.0035	0.0050	0.1072	0.1425
RSD	1.9627%	0.5967%	0.0099%	1.9627%	0.1379%	3.8416%	0.8520%	0.1379%

Method robustness



Validation

Parameter		Requirements of regulatory authorities	Achieved	Result
Selectivity		Baseline separation of anionic irbesartan ingredients	RRT*: Cl^- (0.45), NO_2^- (0.57), PO_4^{3-} (1.26), NO_3^- (1.35)	+
LOD		LOD > 3•SD (blank)	**5 µg/L**	+
LOQ		LOQ > 10•SD (blank)	**30 µg/L**	+
Precision		RSD of peak area, peak height and retention time < 5%	**< 3.9%**	+
Linearity		R^2 > 0.9980 for six-point calibration in the range of 5…100 µg/L	**R^2 = 0.9995**	+
Accuracy		Spike recovery: 80…120%	**99.6…104.0%**	+
Method robustness I	**Temperature variation**	**Selectivity** Baseline separation of irbesartan ingredients	RRT*: Cl^- (0.45), NO_2^- (0.57), PO_4^{3-} (1.31), NO_3^- (1.35)	+
		Precision RSD < 5%	< 0.89 (peak area) < 2.82 (peak hight) < 2.11 (retention time)	+
		Accuracy Spike recovery: 80…120%	**102.1…103.3%**	+
Method robustness II	**Composition of the transfer solution**	**Selectivity** Baseline separation of irbesartan ingredients	RRT*: Cl^- (0.45), NO_2^- (0.58), PO_4^{3-} (1.26), NO_3^- (1.34)	+
		Precision RSD < 5%	< 3.10 (peak area) < 3.10 (peak height) < 0.32 (retention time)	+
		Accuracy Spike recovery: 80…120%	**98.0…103.3%**	+

*RRT = relative retention time, e.g. RRT(Cl^-)= RT(Cl^-)/ RT(N_3^-)

Download a copy of this poster from http://products.metrohm.com (search for 8.000.6010EN).

[1]Micro Devices Metrohm Ltd., 1st Avenue, Indira Nagar, Adyar, Chennai 600020/India, hari@mdml.com, phone +91 44 24452726
[2]Metrohm AG, CH-9101 Herisau/Switzerland, aw@metrohm.com, phone +41 71 353 85 04