Application Note AN-CS-021

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IC assay method validation performed according to USP

Patients may be unable to use commercially available medical formulations for many reasons and therefore require specific compounded formulations [**1**]. Compounded injections of sodium bicarbonate are sterile solutions for correcting metabolic acidosis and other conditions requiring systemic alkalinization [**2**]. Compounded injections of sodium phosphates (a mixture of monobasic and dibasic phosphates [**3**]) serve as a phosphate source to either prevent or correct hypophosphatemia in patients with restricted oral intake. After dilution, these injections can be administered intravenously as electrolyte replenishers. Ion chromatography (IC) with suppressed conductivity detection is the standardized way to accurately quantify sodium in these solutions [**4,5**]. The Metrosep C Supp 2 column was evaluated as an alternative column [**6,7**] in cooperation with the U.S. Pharmacopoeia (USP).

For the equivalence investigation of the Metrosep C Supp 2 - 250/4.0 column, compounded injections were prepared from the respective sodium salts. Anhydrous salts from different manufacturers were used.

Figure 1. Instrumental setup including a 930 Compact IC Flex with the IC Conductivity Detector MB (L) and the 919 IC Autosampler plus (R).

For **sodium bicarbonate compounded injections**, 8.4 g of sodium bicarbonate was dissolved in 100 mL sterile Water for Injection [**4**]. Further manual dilution was performed using ultrapure water (100-fold dilution) to achieve a nominal concentration of 0.23 mg/mL. Sample stock solutions for the **sodium phosphates compounded injections** were prepared from 24 g of monobasic sodium phosphate and 14.2 g of dibasic sodium phosphate – both dissolved in 100 mL sterile Water for Injection. Both solutions were further diluted in ultrapure water (100-fold) to a nominal concentration of 0.92 mg/mL sodium. All samples were prepared as individual duplicates.

A single-point calibration with 0.250 mg/mL of sodium, prepared from sodium chloride in ultrapure water, was used.

EXPERIMENTAL

The samples were injected directly into the ion chromatograph (**Figure 1**) and analyzed using the method parameters given in the respective USP monograph (**Table 1**). Cationic components were isocratically separated on a Metrosep C Supp 2 - 250/4.0 column which contains the alternative packing material L97 (**Figure 2**).

Table 1. IC method parameters as per the USP monographs «Sodium Bicarbonate Compounded Injection» [4] and «Sodium Phosphates Compounded Injection» [5].

Column with L97 packing	**Metrosep C Supp 2 – 250/4.0**
Eluent	8 mmol/L methanesulfonic acid (MSA)
Flow rate	1.0 mL/min
Column temp.	30 °C
Injection volume	10 L
Detection	Conductivity with sequential suppression

A Metrohm Suppressor Module for cation suppression, regenerated with a solution of sodium carbonate and sodium bicarbonate (70 mmol/L each), was used to reduce the background noise in the chromatograms. The conductivity signal was detected after sequential suppression. For the column equivalency study, system suitability (e.g., repeatability, tailing factors) and sample recoveries were evaluated (**Table 2**).

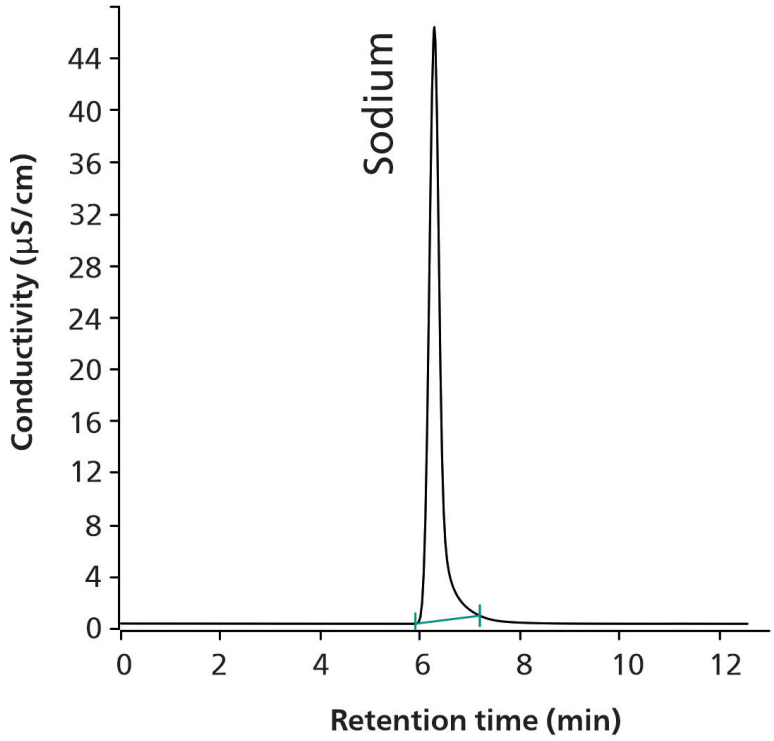

Figure 2. Chromatogram for sodium in a sodium bicarbonate compounded injection containing 0.231 mg/mL sodium (100% recovery).

RESULTS

Sodium bicarbonate and sodium phosphates compounded injection samples, made from the sodium salts from different manufacturers, were analyzed for their sodium content (**Figure 2**) within less than 12 minutes. The IC assay for sodium was conducted according to USP General Chapter <621>, Chromatography [**6**] and fulfilled all suitability and acceptance criteria. Sodium eluted after approximately six minutes as a symmetric peak (tailing factor <1.8). The peak area was highly reproducible (<1.4 % RSD for five replicates, **Table 2**).

Recoveries for the sodium content were determined in the range of 98–102%, within the acceptance criteria of USP.

Table 2. Selected performance characteristics.

Performance characteristics	Acceptance criteria	Results
Tailing factor	Tailing factors (asymmetry) for the sodium peak is NMT 2.0	1.39–1.79
Repeatability	Relative standard deviation for the sodium peak area in the standard solution is NMT 2.0% for five replicates	0.3–1.3%
Accuracy	Average % recovery should be 95.0–105.0% of the manufacturer's CoA value	98–100% sodium in sodium bicarbonate 98–102% sodium in sodium phosphates

CONCLUSION

The presented IC method with the **Metrosep C Supp 2** column that contains the **alternative packing material L97** is a robust, reliable, and validated method suitable to quantify sodium in both **sodium bicarbonate and sodium phosphates compounded injections** according to USP requirements.

REFERENCES

1. *USP General Chapter <797>.* https://www.usp.org/compounding/general chapter-797 (accessed 2023-03-27).
2. Exela Pharma Sciences, LLC. *Sodium Bicarbonate Injection, USP.* dailymed. (accessed 2023-01-16).
3. Fresenius Kabi USA, LLC. *Sodium Phosphates Injection USP.* dailymed. (accessed 2022-07-15).
4. U.S. Pharmacopeia. USP-NF Sodium Bicarbonate Compounded Injection. *Monograph.* https://doi.org/10.31003/USPNF_M10963_04_01.
5. *Sodium Phosphates Compounded Injection.* https://doi.org/10.31003/USPNF_M10964_06_01.
6. *621 Chromatography.* https://doi.org/10.31003/USPNF_M99380_01_01.
7. *1225 Validation of Compendial Procedures*; General Chapter; U.S. Pharmacopeia/National Formulary: Rockville, MD. https://doi.org/10.31003/USPNF_M99945_04_01.

REFERENCES

Internal references: AW IC AE6-0110-032020; AW IC AE6-0131-122020

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CONFIGURATION

930 Compact IC Flex Oven/SeS/PP/Deg

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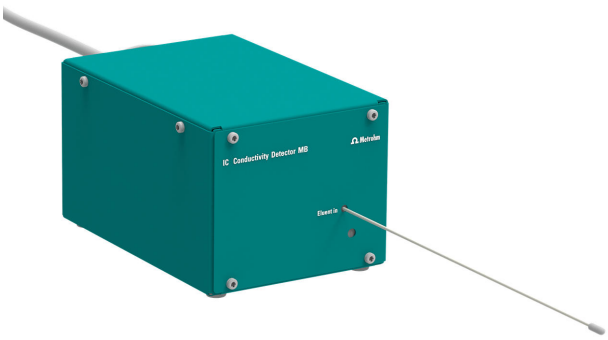

IC Conductivity Detector MB

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- (2mm) ,(IC-MS IC-ICP/MS)

:

- 0 ... 15000 S/cm
- :0.3 L
- X2CrNiMo17-12-2 (316 L) , MSA
- :10.0 MPa (100 bar)
- :20 ... 50 °C, 5 °C
- :< 0.001 °C
- :<°0.2°nS/cm,
- :ID 0.18 mm

MagIC Net 4.1