Improved Quality Control of [^{18}F]FDG: Overcoming Matrix Effects with Advanced Column and Rinsing Strategies.

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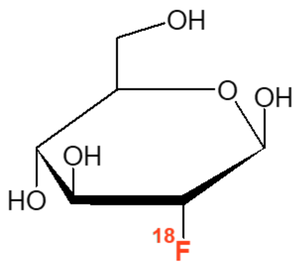

Introduction

High-performance anion exchange chromatography with pulsed amperometric detection (HPAEC PAD) is widely recognized as a powerful technique for the quality control of radiopharmaceutical sugars such as [^{18}F]Fluorodeoxyglucose (FDG). However, using it in daily pharmaceutical practices still proves challenging. Typical FDG formulations contain saline–citrate buffers to ensure physiological pH, isotonic conditions, and stability of FDG, but these components impose a high ionic load on anion-exchange columns. As a result, column capacity is reduced and retention times can shift unpredictably across sequential injections—an unwelcome complication for pharmacopeia-mandated system suitability requirements.

To overcome matrix limitations, we evaluated a new anion-exchange column (SweetSep AEX18) and developed an analytical workflow that complies with regulatory requirements while maintaining chromatographic stability. Pharmacopeial procedures restrict high-ionic-strength rinses during analysis, despite their routine use in carbohydrate HPAEC to ensure column stability. We designed a pharmacopoeia-compliant protocol that allows a post-analysis rinse with sodium methane sulfonate (NaMSA) without affecting QC runtime or system suitability. Using methane sulfonate's strong eluting power and microbial resistance, this method preserves column performance, prevents carryover, and supports long-term reproducibility.

Instrumentation

(I) Antec Scientific ALEXYS FDG Analyzer

- ET210 eluent tray, for sparging and blanketing of eluent with N_2
- P6.1L quaternary LPG pump
- AS6.1L autosampler
- CT2.1 column thermostat
- DECADE Elite, with SenCell™
- DataApex Clarity CDS

(II) Thermo Scientific ICS-6000

- quaternary gradient pump
- Eluent Generator
- Autosampler
- DC-Module with detector
- Thermo Scientific™ Chromeleon™ CDS

Stationary Phase

The SweetSep™ AEX18 stationary phase is developed for high-resolution separation of FDG analysis

- Rugged polymeric anion-exchange resin
- Monodisperse latex-coated particles (5 µm)
- Bifunctional anion exchange sites
- high-resolution separation
- EP conform column diameters (2.1 mm × 185 mm)
- USP conform column diameters (4 mm × 200 mm)

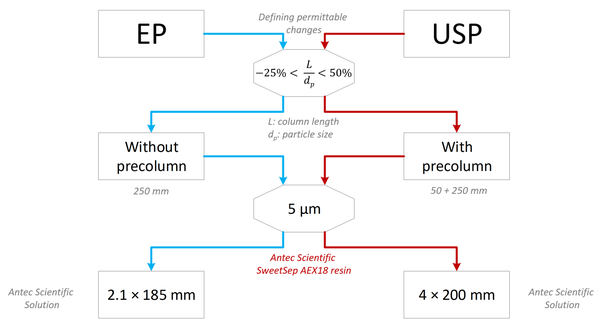

Figure 1: SweetSep AEX18, column formats adjusted to pharmacopeial requirements

Table 1: HPAEC-PAD conditions

HPLC	ALEXYS FDG Analyzer
Columns	SweetSep™ AEX18, 2.1 × 185 mm column, 5 µm;Borate ion trap, 2.1 x 50 mm column, 10 µm
Filter	High-pressure inline filter PEEK, 0.5 µm
Mobile phase	A: 90 mmol/L NaOH B: 90 mmol/L NaOH + 100 mmol/LNaMSA All solutions blanketed with N_2 5.0
Flow rate	0.28 mL/min
System backpressure	≈ 191 bar
Temperature	35°C for separation and detection
Injection volume	2 µL (full loop)
Flow cell	SenCell™ with 2 mm Au WE and HyREF (Pd) RE., AST pos. 2
PAD	Four potential pulse (std.)

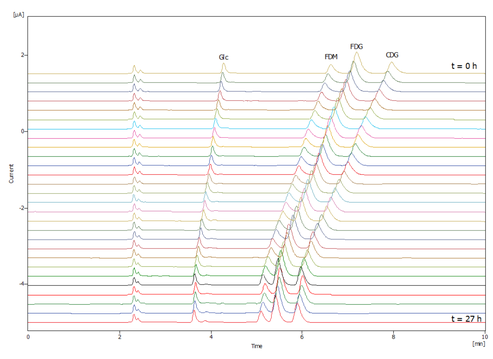

Figure 2: Effect of saline citrate buffer on retention time

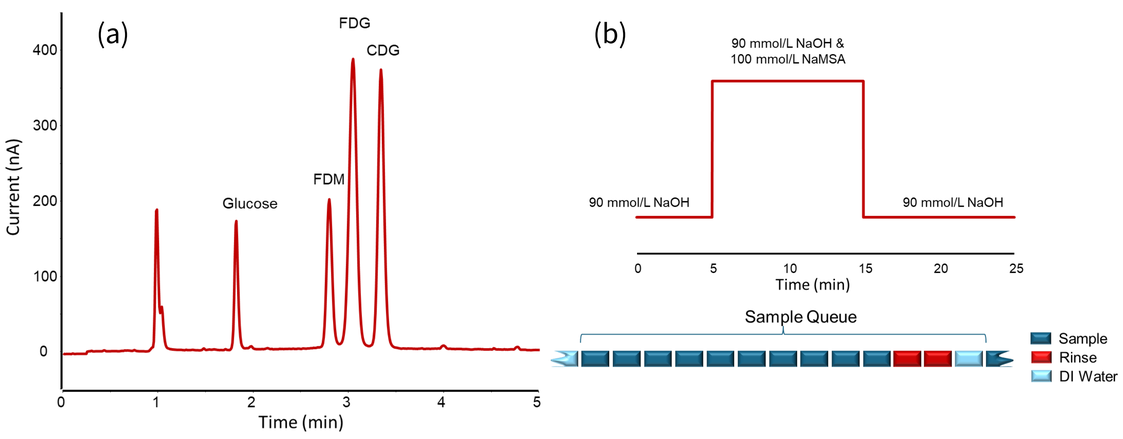

Figure 3: EP compliant (a) separation of Glu, FDM, FDG and CDG, (b) independent rinsing step & sample queue

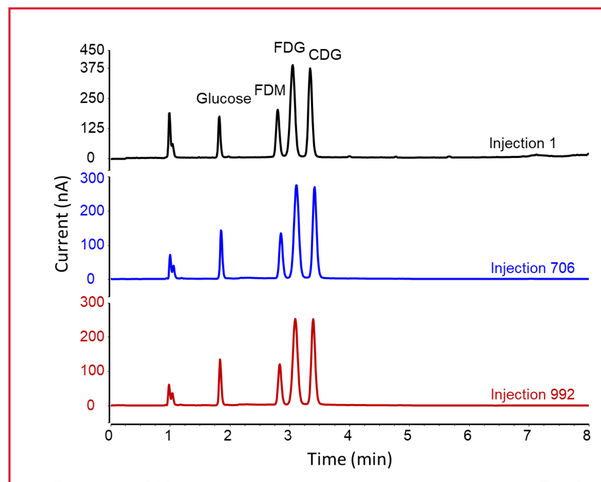

Table 2 Chromatographic Performance (n= 1000)

Criteria	EP	USP*	Found
R_s	>1.5^{FDM}	> 1.0^{FDG}	>1.5^{FDM}; > 1.7^{FDG}
S/N	>10^{FDG}	>50^{CDG}	>300
Tailing		<1.5^{CDG}	< 1.1^{FDM} , <1.1^{FDG}; < 1.1^{CDG}

*) The test was performed with the EP configuration, i.e. 2.1 × 185 mm column w/o guard-column, yet the demanding USP requirements were fulfilled, too.

Figure 4: 1000 consecutive injections, queued according Fig. 2(b)

Table 3: HPAEC-PAD conditions (II)

HPLC	ICS-6000
Columns	SweetSep™ AEX18, 2.1 × 200 mm column, 5 µm w/ precolumn
Mobile phase	EG: 30 mmol/L KOH Pump: 100 mmol/L NaMSA
Flow rate	0.18 mL/min
System backpressure	≈ 180 bar
Temperature	30°C for separation and 25°C for detection
Injection volume	2.5µL (full loop)
Flow cell	ED with 1 mm Au WE and Ag/AgCl RE.
PAD	Four potential pulse (std.)

Table 4 Chromatographic Performance (n= 240)

Criteria	EP	USP*	Found
R_s	>1.5^{FDM}	> 1.0^{FDG}	>1.9^{FDM}; > 1.5^{FDG}
S/N	>10^{FDG}	>50^{CDG}	>100^{FDG}; >80^{CDG}
Tailing		<1.5^{CDG}	< 1.3^{FDM} , <1.2^{FDG}; < 1.3^{CDG}

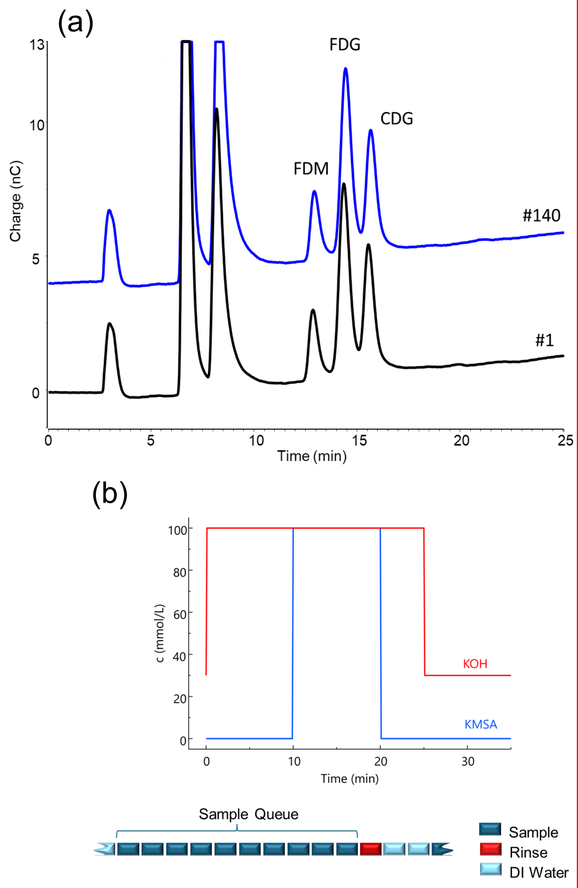

Figure 5: USP compliant (a) separation of Glu, FDM, FDG and CDG, (b) independent rinsing step & sample queue

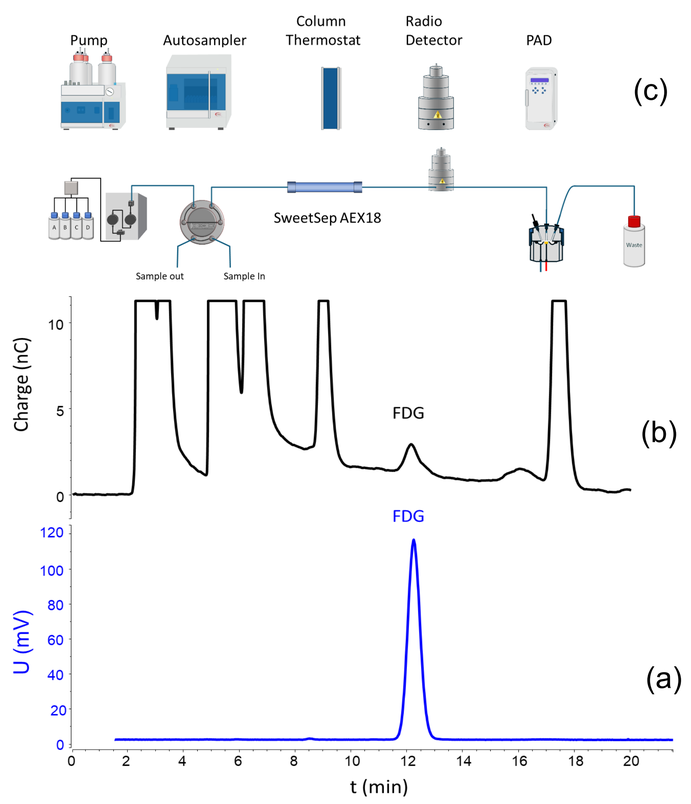

Figure 6: Hot FDG sample (a) scintillation detection, (b) pulsed amperometric detection, (c) schematics of a compliant HPAEC-PAD-Radio Detection Setup; Note: time delay between both detectors compensated.

Conclusion

The results show that using a NaMSA rinse that meets pharmacopeial standards ensures stable FDG HPAEC-PAD performance without increasing the runtime of each run or affecting the QC-release sequence. Both gradient schemes effectively restore the column's performance after saline–citrate loads. The SweetSep AEX18, with its polymeric nanoparticle agglomerate design, minimizes retention-time shifts during sample queues, which is important for unattended operation. NaMSA resists bacterial contamination, is of high purity, and has about two to three times the elution strength of sodium acetate, helping to restore the column's ion-exchange capacity. The workflow allows for manual eluent preparation or the use of Eluent Generation systems, in which the gradient pump delivers the NaMSA rinse, and the generator produces KOH in situ. These options enable long, low-maintenance QC sequences suitable for radiochemistry laboratories.