Continuous Flow Extraction and Analysis of a Single Use Bioprocess System

Kevin Rowland, M.S. and Mark Jordi, Ph.D.
Analytical Services Division; 200 Gilbert St. Mansfield, MA 02048

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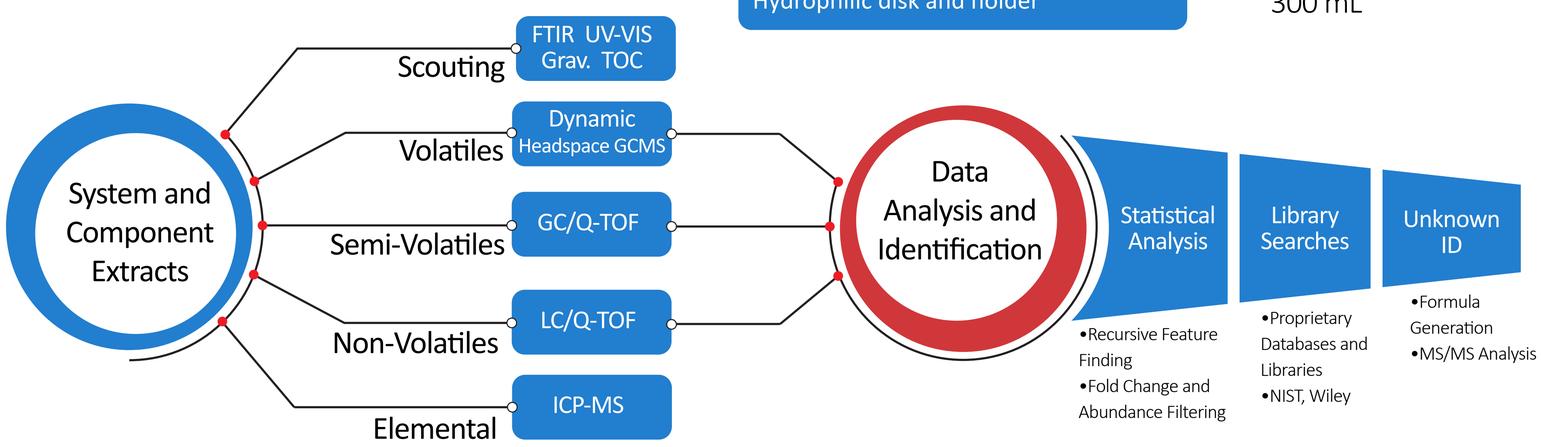
Objective

Single use Bio-processing systems are attractive due to their efficiency and the potential to eliminate complex cleaning procedures and validations. This study was designed to demonstrate an analytical methodology tailored for effective determination of the extractable compounds from a model bioprocess system. A continuous flow extraction was performed in order to investigate the compounds extracted under the conditions most closely representing a use condition. Once compounds had been found and filtered, the effect of standard selection on the number of compounds falling above the analytical evaluation threshold (AET) was investigated.

Analytical Methodology



Model Bioprocess System

Bioprocess Bag
Multilayer Film
LDPE Liquid Contact
EVA Air Barrier Film

Tubing
Phamaceutical grade
Thermoplastic Elastomer
Ultra-pure fluid Processing applications

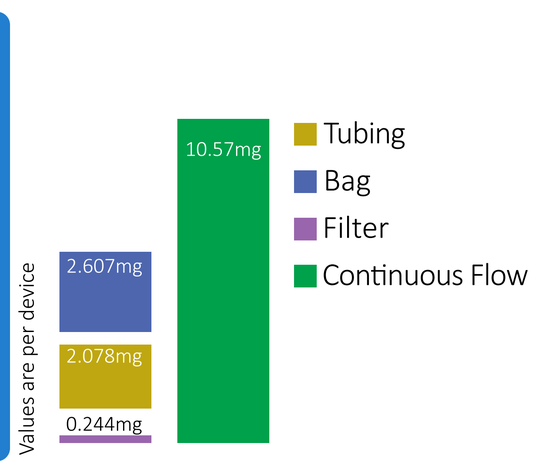
Filter
Hydrophilic disk and holder
Nylon Filter
Polypropylene Housing
Ethylene propylene O-ring

Extraction Vehicle:
Saline- 137mM NaCl, 2.7mM KCl
10 mM Phosphate Buffer (pH 7.4), 300 mL

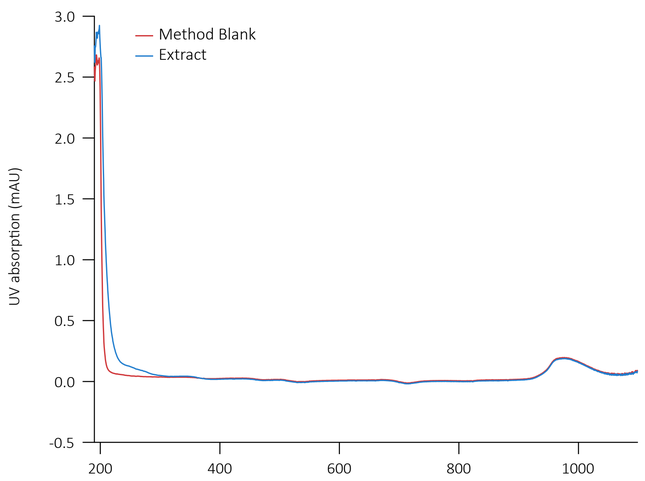
Extraction Conditions:
Continuous recirculation with a perastaltic pump; 72 hours; 37°C

Scouting Analyses

Total Organic Carbon



Spectroscopy



Elemental Analysis

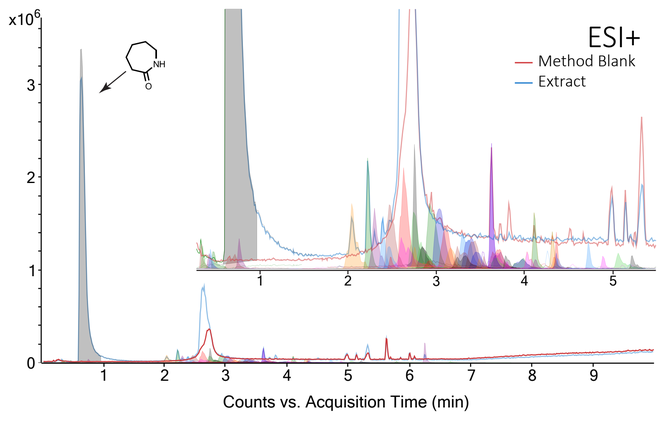
ICP-MS

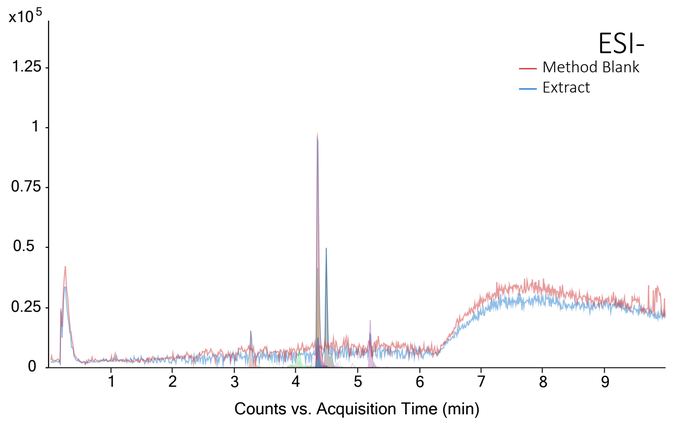
	ng/Device	µg/Day
As	4.5	0.018
Co	25	0.098
Mo	7.8	0.031
Cd	0.6	0.002
Ni	< IDL	
Sb	77	0.31
Hg	5.7	0.023
Cr	12	0.047
Ba	< IDL	
Pb	21	0.084
Na	Matrix	350,000 ng/mL

Values Based on 500 doses per device, 2 doses per day
< IDL - Less than the instrumental detection limit

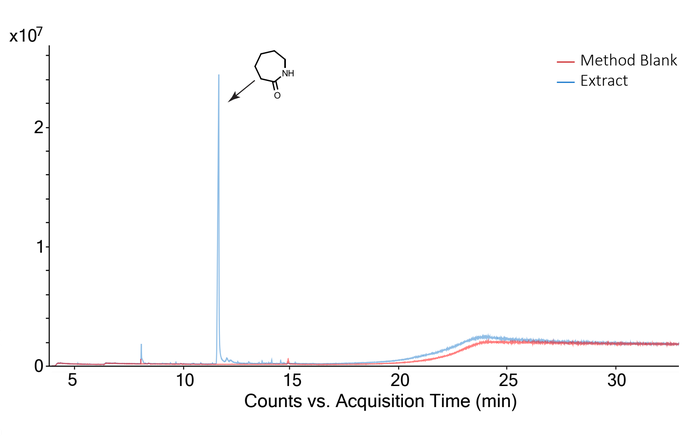
Organic Identification

LC/Q-TOF
Agilent 6545 LC/Q-TOF





GC/Q-TOF
Agilent 7200 GC/Q-TOF



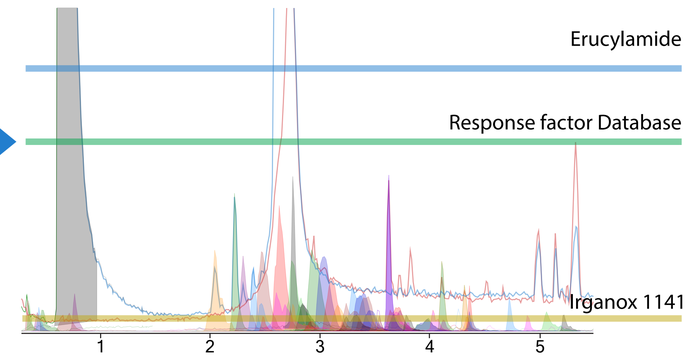
Analytical Evaluation Threshold

$$AET = \left(\frac{SCT}{doses/day}\right) \times \left(\frac{labeled\ doses}{Container}\right) = \frac{0.15\ \mu g}{day} \times \frac{1\ day}{2\ doses} \times \frac{500\ doses}{System} = 37.5\ \mu g/Device$$

Accounting for the extraction performed, the intstrumental limit is: 37.5 µg/Device ÷ 300 mL = 0.125 µg/mL

Norwood D. The Analytical Evaluation Threshold (AET) and Its Relationship to Safety Thresholds, Leachables and Extractables Handbook (2012): 59-78. PQRI.org.

Analytical Standard



Number of compounds observed Above AET depends on Standard Selected

Conclusions

A wide array of analytical techniques are required for thorough identification of system extractables.

Extraction methodology effects the quantity of extractables observed.

The analytical standard used to relate AET concentration to instrument response has a strong effect on the response cut-off.

PQRI recommendation of adjusting the AET by the greater of 50% or the %RSD of the relative response factor database represents good compromise.