Strategies for Determination of Elemental Impurities in Complex Samples

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## P&G Products Impacted

<table>
<thead>
<tr>
<th>Category</th>
<th># of “Drug” Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal Health</td>
<td>~100</td>
</tr>
<tr>
<td>Oral Care</td>
<td>~150</td>
</tr>
<tr>
<td>Beauty</td>
<td>~240</td>
</tr>
<tr>
<td>Household Care</td>
<td>~10</td>
</tr>
</tbody>
</table>

### Product Types
- Probiotics
- Fiber Supplements
- GI OTC Medicines
- Cough/Cold Medicine
- Mouthwash/Rinse
- Toothpaste
- Antiperspirants
- Antidandruff Shampoo
- Color Cosmetics (SPF)
- Skin Care (SPF)
- Antibacterial Soap

### Forms
- Tablets/Capsules
- Powders
- Oral Liquids
- Drops/Sprays
- Pastes/Gels
- Bars/Soaps
- Creams/Lotions
- Sticks/Roll-Ons
Analytical Challenges

Diverse Products

- **Daily consumption range:** < 200 mg – 250 g
  - 100% (medicines, leave-on treatments)
  - 5-10% (inadvertent swallowing, “habits & practices”)
  - 1% (“rinse-off” products, shampoo, soap)

- **Product composition**
  - **Excipients:** Salts, minerals, botanicals, organics, polymers
  - **Actives:** Bismuth subsalicylate, TiO$_2$, ZnO, SnF$_2$, NaF, SeS$_2$, Zn pyrithione, Al/Zr based actives
  - **Proportions:** < 1% to 95% of finished product
  - **Co-mingled:** Trace EIs and inorganic RMs

Multielemental Analysis

- **Class 1 (As, Cd, Hg, Pb) & 2a (Co, V, Ni) + catalysts**
  
  *Exposure: mainly peroral and topical*

- Quantitate all elements in one analysis
Available Instrumentation

Milestone UltraWAVE with ECR (HCl compatible)

SCP Hot blocks

Milestone UP

Perkin Elmer Elan DRCII ICP-MS

Perkin Elmer Optima ICP-OES

Bruker Tiger S8 WD-XRF

Agilent 7900 ICP-MS

Agilent 8800 QQQ ICP-MS
P&G’s Current “Platinum Standard”

- **Total Digestion**
  - High throughput (n=15)
  - Multiple digestion matrices in same batch/run

- Multielemental, sensitive, highly selective analysis
  - ICP-MS/MS
  - Multiple collision/reaction modes

**Best-Available Screening Assurance**

*Most efficient approach to large number of products/materials*
Example: Bismuth Subsalicylate Oral Suspension containing magnesium aluminum silicate

**Digestion**

**Daily Dose**: up to ~ 250 g

**Matrix Effects**

**Corresponding Concentration Limits** (per USP <232> PDEs)

- As: 60 ppb
- Cd: 20 ppb
- Hg: 120 ppb
- Pb: 20 ppb
- Co: 200 ppb
- Ni: 800 ppb
- V: 400 ppb

**Sensitivity**

**Active**: Bismuth Subsalicylate (BSS)

- Bi: m/z 209; Pb: m/z 206, 207, 208

**Specificity**
Specificity: Quantitating Pb in BSS Materials

- Natural variation, quantify Pb as sum of isotopes
- $^{209}$Bi$^+$ is massive relative to Pb; “fronts” into $^{208}$Pb$^+$

**Remedy**

Use MS/MS
Risk Assessment
- Survey finished products by formulation family
- Minimally quantitate Class 1 & 2a EIs
- Time-of-use verifications

Identify Sources
- Evaluate RMs for sources of EIs
- Determine variability of method/material
- Set RM specifications for control of EIs

Control Measures
- RM specifications for targeted EIs
- Methodology optimization
- Full validation per <233>

Implementation
- Deploy methods to plant
- Release testing of RMs

Meet PDE Limits

Near or above control threshold

Below control threshold

Reformulate
Risk Assessment Methodologies

Survey products by formulation family

Minimally quantitate Class 1 & 2a EIs
  • Complete digestion
    “total content” assessment
  • Multielemental, sensitive, highly selective
  • LOQ minimally 10% of PDE

Time-of-use verification (typical minimums)
  • Calibration: multiple point curve; low std determines LOQ
  • Controls: digestion blanks, second source standards
  • Variability: replicates (n=3)
  • Accuracy & precision: pre-digestion spikes in matrix (n=3)

*Full validation per USP <233> not practical (or necessary) for risk assessments*
Why Do Total Digestions?

- USP <233> asks for it
- Most straightforward approach to EIs
- Deployability: Consistency/enforcement
- Optimal robustness and precision

**Lot-to-Lot Variability**
- Total Digestion 6.6% RSD
- Acid Leach 12% RSD
- Recovery 54%

**Total digestion vs acid leach**

<table>
<thead>
<tr>
<th>Lots of Silicate Material</th>
<th>Pb Concentration (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.5</td>
</tr>
<tr>
<td>2</td>
<td>11.2</td>
</tr>
<tr>
<td>3</td>
<td>9.7</td>
</tr>
<tr>
<td>4</td>
<td>10.3</td>
</tr>
<tr>
<td>5</td>
<td>12.0</td>
</tr>
<tr>
<td>6</td>
<td>13.5</td>
</tr>
<tr>
<td>7</td>
<td>14.2</td>
</tr>
</tbody>
</table>
Key to Total Digestion Approaches

- Choose the appropriate digestion matrix
  \[ \text{HNO}_3, \text{H}_2\text{O}, \text{HCl}, \text{HF}, \text{HBF}_4, \text{H}_3\text{PO}_4 \]

- Prevent formation of insoluble fluorides with HBF$_4$
  - Many silicates/products also contain Mg, Al, Ca, etc.
  - *Ultra-trace HBF$_4$ not commercially available*
    - Complex excess fluoride with boric acid (2 step process)
    - Prepare ultra-trace HBF$_4$ from HF & boric acid

- Stabilize the analyte(s)
  - Hg: Au, HCl
  - Sb, Sn: HF, HCl

*Not just “Nuking Sample”…*
For products, leverage...
- Material knowledge
- Product chemistry

_Titrate digestion matrix to most complex ingredient_
Risk Assessment: Quantitate Class 1 & 2a EIs

Generic product: Minerals (silicates), Metal based active

**Excellent precision**

\( n=3 \) replicate preparations

\( RSD < 5\% \)

- HNO\(_3\) + HBF\(_4\) in Microwave
  - Complete digestion
- ICP-MS/MS analysis
  - Sensitivity
  - Matrix effects
  - Specificity
Risk Assessment: Accuracy

Generic product: Minerals (silicates), Metal based active

Need robust measure of incurred levels for assessment of accuracy

Pre-digestion spikes ≤ PDE limit
n=3 replicates

Incurred levels
Risk Assessment: Accuracy

Generic product: Minerals (silicates), Metal based active

Excellent accuracy even with incurred levels
Mean recovery (n=3): 92-103%
RSDs: 0.7%-5.1%
Identify Sources of EIs

Evaluate RMs for sources of EIs
- Total digestion
- Multielemental, sensitive, high specificity

**Goal: Obtain mass balance**

Determine variability of method/material
- Analyze high number of lots
- Evaluate alternate suppliers/grades

Set RM specifications for control of EIs

*Most Extreme Capability Requirements*
*Digestion, Matrix Effects, Specificity*
Mass Balance from RM

Calculate exposure contribution from each RM

Confidently identify sources of Els (per element of concern)
Setting Specifications for RMSS

<table>
<thead>
<tr>
<th>Raw Materials</th>
<th>Product A</th>
<th>Product B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silicate</td>
<td>[Exposure]</td>
<td>[Exposure]</td>
</tr>
<tr>
<td>Active Salt</td>
<td>[Exposure]</td>
<td>[Exposure]</td>
</tr>
<tr>
<td>Mineral</td>
<td>[Exposure]</td>
<td>[Exposure]</td>
</tr>
</tbody>
</table>

Maximum contribution if at specification

Exposure (µg/day)

PDE
Strategies for **Control Measures**

RM specifications for targeted EIs
- Identified as problematic in previous stages
- Quantitative methods for on-going control

Methodology optimization
- “State-of-the-art” to common platforms
  - **Goal:** Maintain accuracy and specificity
- Consider complete/exhaustive extractions (without HF/HBF₄)
  - **Goal:** Equivalent to total digestion
- Optimize the collision/reaction cell modes as needed
- Cross validate various approaches

Full validation per USP <233>
- Include alternate preparations where possible
- Demonstrate multiple collision/reaction cell modes
Digestion Optimization – Silicate

Mean Comparison: 98.9%

Total Digestion
- HNO₃, H₃PO₄, HBF₄
- Precision (n=12): 1.6% RSD
- Mean accuracy (n=12): 100.8%
- Solution stability: 20 days

Complete/Exhaustive Extraction
- HNO₃, H₃PO₄
- Precision (n=3): 0.7% RSD
- Solution stability: 20 days

![Bar chart showing Pb Concentration (ppm) vs Lot Number.](chart.png)
Digestion Optimization – Talc

**Mean Comparison:** 104.5%

**Total Digestion**
- HNO₃, HCl, HBF₄
- Precision (n=12): 3.3% RSD
- Mean accuracy (n=12): 101.0%
- Solution stability: 18 days

**Complete/Exhaustive Extraction**
- HNO₃, HCl
- Precision (n=3): 11% RSD
- Solution stability: 1 day

*Lose flexibility*

Doesn’t work for all EIs

**55% Recovery**

**Pb Concentration (ppm) V Concentration (ppm)**
Digestion Strategies at Each Stage

**Risk Assessment**
- Total digestion
  - Straightforward compliance
  - Efficient (large #’s)
  - Improved methodology

**Identify Sources**
- Near or above control threshold
- Total digestion
  - Mass balance
  - Material variability
  - Efficient (large #’s)

**Control Measures**
- Below control threshold
- Total digestion
  - Complete extraction* (targeted EI)

**Implementation**
- Total digestion
  - Complete extraction* (targeted EI)

*If equivalent to total digestion

Meet PDE Limits
Acknowledgements

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