Universal Approach in the Determination of Extractable and Leachable Metals in Pharmaceutical Products by ICPMS

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ABSTRACT

A universal approach for determining the extractable and leachable metals in pharmaceutical products by Inductively Coupled Plasma Mass Spectrometry (ICPMS) is investigated. This study examines digestion strategies of both packaging materials and formulated products for complete trace metals analysis. Packaging materials and drug products are evaluated for leachable metals by stressing the materials under accelerated stability conditions. Trace metal profiles of 64 elements for several different types of packaging materials and some common pharmaceutical products are reported.

The classical approach to Controlled Extractables analysis is to expose the material to a specific solvent (ie. water, organic, buffer)[1] for a period of time at an elevated temperature and measure the trace metal content. While this technique is useful, it is limited by the quantitation limit (QL) of each metal and the volume and nature of solvent used. Also, certain metals at extremely low levels may not be detected, thus there is the potential for their presence in the drug product to go unnoticed.

The universal approach involves a complete acid digestion of the packaging material and drug product. Sample solutions are then analysis by ICPMS. This combination provides reduced sample preparation time, increased sensitivity and a complete metals profile as the ICPMS provides for elements not typically measured by optical emission ICP. Based upon the nature of these materials and potential metals, a selection tree was developed for the appropriate type of digestion and acid mixture for several different materials and some common pharmaceutical products. Exposure of the packaging material and drug product at accelerated stability conditions then provides information into any extractable or leachable that has migrated from the packaging into the drug formulation.

RATIONALE

The focus in Pharma for extractables and leachables tends to be in the organic area, in which pharmaceutical products are evaluated for organic components which may migrate to the product. This paper however investigates the equally important area of inorganic analysis with regard to this concept.

Metals are known to have either a toxic effect based on certain elements (ie. Al, Cd, Cr, Cu, Pb, Mn, Zn)[2] or can contribute to interactions between APIs and excipients (ie. Fe, Zn, Cu, Mn)[3].

A comprehensive method of evaluating the entire metals profile then provides a more effective means to determine the potential metal extractables and leachables over current limited extraction techniques.

The concept of a universal or comprehensive method of analysis for trace metals is based upon evaluating the material of interest for all potential contaminates. Unfortunately, trace metal limits and toxicity data (Fig. 1) can be confusing, as limits and toxicity is reported in literature relative to such things as drinking water or as an exposure limit as an air contaminate. [5,6,7,8]

Fig. 1 - Trace Metal Limits and Toxicity Data

Element	EPA Limits (ppm)	PEL mg/m^3	LD50 mg/Kg (Oral/Acute)
Aluminum (Al)	0.05	15	None
Antimony (Sb)	0.006	0.05	7000(rat)
Cadmium (Cd)	0.005	0.003	2330(rat)
Chromium (Cr)	0.1	1	
Copper (Cu)	1	1	None
Iron (Fe)	0.3	10	
Lead (Pb)	0.02	0.05	None
Manganese (Mn)	0.05	5	
Nickel (Ni)	0.02*	1	
Zinc (Zn)	5	15	

* WHO (World Health Organization) guidelines
None – no data or limit is currently available

EXPERIMENTAL

Equipment

- Perkin Elmer ELAN 9000 ICP-Mass Spectrometer

Materials

- Clear glass
- Rubber lyophilization/septum stoppers
- HDPE, polyester and polycarbonate bottles
- Commercial RTE baby food in unspecified packaging
- 0.45% sodium chloride for inhalation - polypropylene bottle

Fig. 2 - Trace Metal Profile of Clear Glass Nitric/HF Digestion

Analyte	Result (µg/g)	Analyte	Result (µg/g)
Ag	**< 0.1**	Na	2.4%
Al	**1.6%**	Nb	0.4
As	**0.3**	Nd	0.4
Au	< 0.1	**Ni**	**< 0.1**
B	**5.5%**	P	< 0.1
Ba	**21**	**Pb**	**1.0**
Be	**< 0.1**	**Pd**	**1.6**
Bi	**0.1**	Pr	0.5
Ca	361	**Pt**	**< 0.1**
Cd	**0.5**	Re	< 0.1
Ce	8.8	Rh	< 0.1
Co	< 0.1	Ru	< 0.1
Cr	**0.2**	**Sb**	**0.5**
Cs	< 0.1	Sc	< 0.1
Cu	**0.1**	**Se**	**0.1**
Dy	< 0.1	Si	> 30%*
Er	< 0.1	Sm	< 0.1
Eu	< 0.1	**Sn**	**< 0.1**
Fe	**239**	Sr	1.7
Ga	1.2	Ta	< 0.1
Gd	< 0.1	Tb	0.2
Ge	0.5	Te	< 0.1
Hf	6.0	Th	0.2
Ho	< 0.1	Ti	6.7
In	< 0.1	**Tl**	**< 0.1**
Ir	0.2	Tm	< 0.1
K	0.1%	U	0.3
La	2.5	V	< 0.1
Li	0.2	W	0.1
Lu	< 0.1	Y	2.8
Mg	61	Yb	0.1
Mn	**0.2**	**Zn**	**< 0.1**
Mo	**4.8**	Zr	206

* Si value obtained by FLAA

Fig. 3 - Trace Metal Profile of Butyl Rubber (Grey) Lyo/Serum Stopper Three Acid Digestion

Analyte	Result (µg/g)	Analyte	Result (µg/g)
Ag	**< 0.1**	Na	87
Al	**0.13 %**	Nb	< 0.1
As	**3.0**	Nd	1.7
Au	< 0.1	**Ni**	**1.0**
B	**1.7**	P	43
Ba	**3.6**	**Pb**	**1.1**
Be	**< 0.1**	**Pd**	**< 0.1**
Bi	**< 0.1**	Pr	0.4
Ca	640	**Pt**	**< 0.1**
Cd	**< 0.1**	Re	< 0.1
Ce	< 1	Rh	< 0.1
Co	0.2	Ru	< 0.1
Cr	**2.6**	**Sb**	< 0.1
Cs	< 0.1	Sc	< 0.1
Cu	**2.3**	**Se**	< 0.1
Dy	0.4	Si	14
Er	0.2	Sm	0.3
Eu	< 0.1	**Sn**	**0.7**
Fe	**325**	Sr	25
Ga	0.1	Ta	< 0.1
Gd	0.4	Tb	< 0.1
Ge	< 0.1	Te	< 0.1
Hf	< 0.1	Th	0.2
Ho	< 0.1	Ti	0.81 %
In	< 0.1	**Tl**	**< 0.1**
Ir	< 0.1	Tm	< 0.1
K	117	U	0.1
La	2.0	V	1.3
Li	9.3	W	< 0.1
Lu	< 0.1	Y	1
Mg	0.93 %	Yb	< 0.1
Mn	**7.8**	**Zn**	**81**
Mo	**< 0.1**	Zr	0.7

DISCUSSION AND RESULTS

The decision tree provided illustrates a systematic approach to digesting and analyzing many different types of materials for trace metals using simple to complex acid digestions.

The universal approach (complete digestion) lends itself to a vast and diverse set of packaging materials, trace metals and pharmaceutical products. Current extraction techniques such as USP <381> do not accurately reflect the entire trace metals profile, as extraction by autoclave or other solvent, then measuring turbidity, pH, heavy metals (as Pb) and then residue weight can not provide the same level of information as a complete trace metals profile nor does this information provide any indication of toxicity or potential metal/product interaction.

Simply extracting materials with a series of solvents may not provide the entire profile of trace metals, which are potentially harmful. However, using the universal approach, a formulator could evaluate or screen a series of packaging materials for total metals content.

In the examples provided, a sample of clear glass (Fig. 2) and a butyl rubber serum stopper (Fig. 3) were completely acid digested and analyzed. As can be seen in the data, significant levels of elements such as aluminum (Al), boron (B), barium (Ba), calcium (Ca), iron (Fe), potassium (K), magnesium (Mg), sodium (Na), silicon (Si), strontium (Sr), titanium (Ti), zinc (Zn) and zirconium (Zr) were found.

Then using this type of total metal data, extractable or leachable levels using drug product or solvents similar in nature to the final product could predict the feasibility of using the packaging materials with the drug product. Selective metals of interest can now be monitored, instead of tracking the entire series of metals.

Fig. 4 - Comparison of Digestion vs. Extraction
HDPE bottle (Ti Filler)

Element	Digestion (μg/g)	Water (μg/g)	0.1N HCl (μg/g)	Buffer[1] (μg/g)
Al	89	< 1	9	24
Ca	8	< 1	< 1	7
Fe	5	< 1	< 1	< 1
Sn	3	< 1	1	< 1
Ti	3855	< 1	< 1	< 1
Zn	214	29	20	55

[1] 2% Citric Acid

Fig. 5 - Comparison of Digestion vs. Extraction Laminated Bottles

Element	Polyester Bottle		Polycarbonate Bottle	
	Digestion (μg/g)	Buffer[1] (μg/g)	Digestion (μg/g)	Buffer[1] (μg/g)
Ca	21	14	12	5
Fe	2	< 1	< 1	< 1
Sb	151	7	< 1	< 1
Sn	1	< 1	< 1	< 1
Ti	16	< 1	< 1	< 1
Zn	10	4	13	2

[1] 2% Citric Acid

Examples of this concept are seen in digestion versus extraction studies of HDPE bottles (Fig. 4) and Polyester/Polycarbonate bottles (Fig. 5). As shown with the HDPE bottle, a significant amount of titanium (Ti) is present in the digested bottle, yet none of the three extraction solvents indicated levels of Ti. Also, significant levels of aluminum (Al) and zinc (Zn) are seen in this bottle and while Al is not extracted with water, the levels extracted with acid and buffer definitely indicate a toxicity issue. Zinc levels with all of the extractions indicate a potential issue.

In the laminated bottles, levels of antimony (Sb), calcium (Ca), zinc (Zn) and titanium (Ti) are reported, yet the extraction buffer (2% citric acid) was somewhat similar for a few of the elements, but clearly did not indicate the potential for Sb to be present in future formulations. Again, an element such as calcium may not present a toxicity issue in this case, however it may complex with the product, thus changing the solubility parameters and potentially efficacy.

Again, classic approaches to extractable and leachable (E/L) studies may not be appropriate as some metals (ie. Os, Co) are practically insoluble in water. Metals such as palladium, platinum and tin are used extensively as catalysts. However, the inorganic forms of these elements are relatively non-toxic versus the more soluble salt forms or organic forms. Again, extraction of these metals may not occur based on the solvent system selected.

This is not to say that extraction of materials with different solvent systems is not useful. In fact, these experiments indicate levels of metals that potentially can be extracted or leach into a specific pharmaceutical product. However, in most cases, the specific metals and initial levels contained within the packaging materials or container are unknown. This type of information can be useful in setting vendor specification for packaging materials.

An example of this is shown with a commercially available baby food product (Fig. 6), in which the polypropylene(PP) when digested was found to contain levels of lithium (Li). This material was stressed for 3 months at 40°C and the digested product did not indicate any leaching of the Li.

Also, levels of Al, Fe, Ni and Zn were found, which may indicate issues related to both toxicity and metal/product interactions.

The baby food was selected as this product contained a significant amount of citric acid, which has been demonstrated in our laboratories to be an effective solvent in extraction of metals from packaging materials.

Fig 6. - Trace Metal Profile
Digested RTE Baby Food and Packaging ♷7 OTHER

Analyte	Result (ppb) Container*	Result (ppb) Food*	Analyte	Result (ppb) Container*	Result (ppb) Food*
Ag	< 10	< 10	Na	3.1**	3.5**
Al	**663**	**35**	Nb	< 10	< 10
As	< 10	< 10	Nd	< 10	< 10
Au	< 10	< 10	**Ni**	**492**	**158**
B	< 0.1	6.0**	P	1.9**	252**
Ba	19.1	110	Pb	12.5	< 10
Be	< 10	< 10	Pd	< 10	< 10
Bi	< 10	< 10	Pr	< 10	< 10
Ca	9.1**	15.6**	Pt	< 10	< 10
Cd	< 10	< 10	Re	< 10	< 10
Ce	< 10	< 10	Rh	< 10	< 10
Co	24	< 10	Ru	< 10	< 10
Cr	254	483	Sb	< 10	< 10
Cu	< 10	582	Sc	< 10	< 10
Dy	< 10	< 10	Se	< 10	< 10
Er	< 10	< 10	Si	7.6**	8.8**
Eu	< 10	< 10	Sm	< 10	< 10
Fe	**3188**	**1473**	Sn	19.4	< 10
Ga	< 10	< 10	Sr	< 10	278
Gd	< 10	< 10	Ta	< 10	< 10
Ge	< 10	< 10	Tb	< 10	< 10
Hf	< 10	< 10	Th	< 10	< 10
Ho	< 10	< 10	Ti	< 10	32
In	< 10	< 10	Tl	< 10	< 10
Ir	< 10	< 10	Tm	< 10	< 10
K	7.8**	0.22%	U	< 10	< 10
La	< 10	< 10	V	< 10	< 10
Li	**102****	**< 10**	W	< 10	< 10
Lu	< 10	< 10	Y	< 10	< 10
Mg	534	124**	Yb	< 10	< 10
Mn	25	450	**Zn**	**20.0****	**1472**
Mo	< 10	< 10	Zr	< 10	< 10

*Product stored at 40C for 3 months
** Concentration in ppm

Fig 7. - Trace Metal Profile
Digested PP bottle and NaCl Solution (neat)

Analyte	Result (ppb) Container	Result (ppb) Solution	Analyte	Result (ppb) Container	Result (ppb) Solution
Ag	**34**	**2.2**	Na	4510	NQ
Al	1095	< 0.1	Nb	< 10	< 0.1
As	< 10	11.5	Nd	< 10	< 0.1
Au	< 10	0.1	**Ni**	**30**	**0.5**
B	< 10	0.4	P	5600	< 0.1
Ba	68	< 0.1	Pb	< 10	< 0.1
Be	< 10	< 0.1	Pd	< 10	< 0.1
Bi	< 10	< 0.1	Pr	< 10	< 0.1
Ca	**7360**	**55**	Pt	< 10	< 0.1
Cd	< 10	< 0.1	Re	< 10	< 0.1
Ce	< 10	< 0.1	Rh	< 10	< 0.1
Co	< 10	< 0.1	Ru	< 10	< 0.1
Cr	**183**	**1.2**	Sb	< 10	< 0.1
Cu	**520**	**69**	Sc	< 10	< 0.1
Dy	< 10	< 0.1	Se	18	< 0.1
Er	< 10	< 0.1	**Si**	**3350**	**128**
Eu	< 10	< 0.1	Sm	< 10	< 0.1
Fe	**724**	**0.7**	Sn	15	< 0.1
Ga	< 10	0.1	**Sr**	**11**	**0.9**
Gd	< 10	< 0.1	Ta	< 10	< 0.1
Ge	< 10	< 0.1	Tb	< 10	< 0.1
Hf	< 10	< 0.1	Th	< 10	< 0.1
Ho	< 10	< 0.1	Ti	76	< 0.1
In	< 10	< 0.1	Tl	< 10	< 0.1
Ir	< 10	< 0.1	Tm	< 10	< 0.1
K	< 10	10.4	U	< 10	< 0.1
La	< 10	< 0.1	V	< 10	22
Li	48	< 0.1	W	< 10	< 0.1
Lu	< 10	< 0.1	Y	< 10	< 0.1
Mg	**530**	**7.8**	Yb	< 10	< 0.1
Mn	11	< 0.1	Zn	1588	< 0.1
Mo	< 10	< 0.1	Zr	< 10	< 0.1

DISCUSSION AND RESULTS (Cont'd)

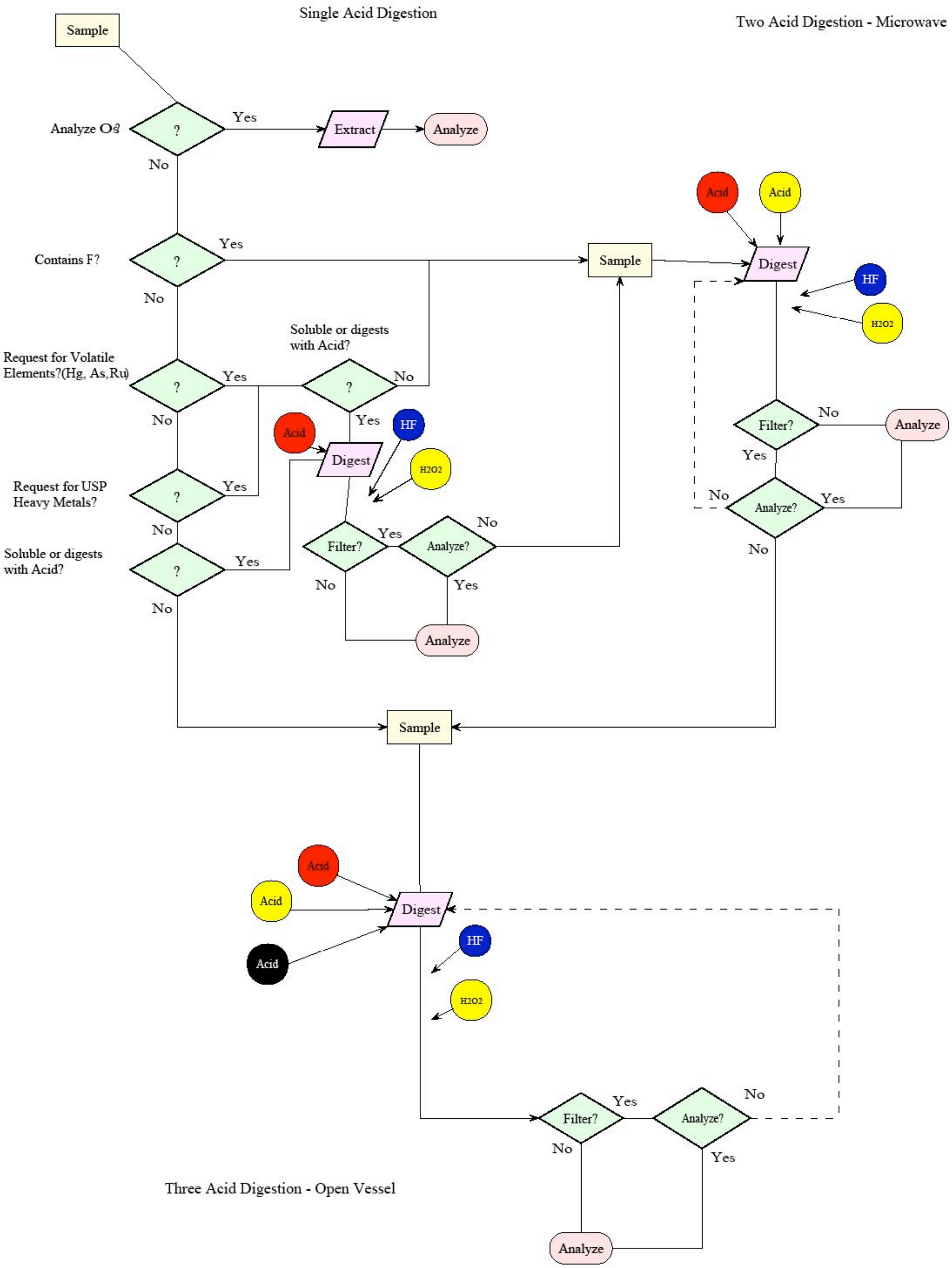
Finally, sodium chloride solution (Fig. 7) was analyzed from a polypropylene bottle, which indicated metals (Ag, Ca, Cr, Cu, Fe, Mg, Ni, Si and Sr) that may have leached from the packaging into the NaCl solution.

Again, these elements may indicate issues related to both toxicity and metal/product interactions.

SUMMARY

This work has shown that a universal approach to Controlled Extractables can be useful :

- in the evaluation of product safety
- in the evaluation of potential product containers and closures
- in the evaluation and setting of vendor specifications
- in the demonstrating that Controlled Extractables can be leached into various products.



Single Acid Digestion
Two Acid Digestion - Microwave
Sample
Analyze Os?
?
Yes
No
Extract
Analyze
Contains F?
Sample
Digest
Acid
HF
H2O2
Request for Volatile Elements?(Hg, As,Ru)
Soluble or digests with Acid?
Request for USP Heavy Metals?
Filter?
Analyze?
Three Acid Digestion - Open Vessel

Intertek

REFERENCES CITED

1. United States Pharmacopeia (USP30-NF25), General Tests and Assays <381> Elastomeric Closures for Injections.

2. Fliszar, K.A.; Walker, D.; Allain, L. Profiling of Metal Ions Leached from Pharmaceutical Packaging Materials. *PDA J. Pharm. Sci. Technol.* **2006,** 60 (6), 337-342.

3. Fliszar, K.A.; Walker, D.; Allain, L. Profiling of Metal Ions Leached from Pharmaceutical Packaging Materials. *PDA J. Pharm. Sci. Technol.* **2006,** 60 (6), 337-342.

4. United States Environmental Protection Agency (EPA), Drinking Water Contaminates, US EPA website www.epa.gov/safewater/contaminants

5. Occupational Safety and Health Administration (OSHA), 29 CFR 1910.1000 Table Z-1, OSHA website www.osha.gov

6. World Health Organization (WHO), Inorganic Tin in Drinking-water Background document for development of WHO Guidelines for Drinking-water Quality, **2004**, publication WHO/SDE/WSH/03.04/115, pp. 1-6.

7. World Health Organization (WHO), Molybdenum in Drinking-water Background document for development of WHO Guidelines for Drinking-water Quality. **2003**, publication WHO/SDE/WSH/03.04/11, pp. 1-7.

8. Hoekstra, E.J: Trincherini, P.R; Pedroni, V.; Passarella, R.; Rieth, F.; Savolainen, R; Elements in tap water Part 1 – Initial sampling and measurements. EC DG Joint Research Centre, Institute for Environment and Sustainability, Inland and Marine Waters Unit. **2003,** publication EUR 20672 EN, pp. 1-31.

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