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ANALYSIS OF ELEMENTAL IMPURITIES BY WDXRF IN PHARMACEUTICALS AND DIETARY SUPPLEMENTS

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STATE OF THE ART

Current requirements introduced by European Medicines Agency (EMA) and United States Pharmacopeia (USP) for **measurement of elemental impurities in drug products** present a challenge to the capacity of existing analytical procedures for the monitor of these impurities **in the ppm range** (Table 1).

Table 1. Current EMA and USP limits for metals impurities in pharmaceuticals (oral route) [1,2]

EMA		USP 38	
Classification of elements	Concentration (ppm)	Element	Concentration (ppm)
Class 1A		As[b]	0.15
Pt, Pd	10	**Pb**	0.5
		Hg[b]	1.5
Class 1B		**Cd**	2.5
Ir, Rh, Ru, Os	10[a]	**Ir**	10
		Mo	10
Class 1C		**Os**	10
Mo, Ni, Cr, V	25	**Pd**	10
		Pt	10
Class 2		**Rh**	10
Cu, Mn	250	**Ru**	10
		V	10
		Ni	50
Class 3		**Cu**	100
Fe, Zn	1300	**Cr**	*

[a] Combination of the 4 elements should not exceed the specified limit; [b] inorganic; * not a safety concern

ICH-Q3D document does not impose any sample preparation method or instrumental technique, but USP<233> and EP2.4.20 chapters list suitable techniques for metal impurities testing (ICP-AES, ICP-OES, AAS and XRFS). [3-5] However, such techniques have elevated costs and require numerous reagents, the destruction of the matrix by acids mixtures, with risk of cross-contamination or element losses due to incomplete solubilization or volatilization. [6,7]

According to USP, any alternative technique is considered acceptable and equivalent to those procedures, provided that has been validated and meets the acceptance criteria. [4]

WORK PURPOSES

- To **validate an analytical procedure based on WDXRF spectrometry** for the **determination of 16 elemental impurities (As, Cd, Cr, Cu, Hg, Ir, Mn, Mo, Ni, Os, Pb, Pd, Pt, Rh, Ru and V) in powdered pharmaceuticals** according to international regulatory guidelines;
- To **monitor the concentration of these impurities in conventional medicines and dietary supplements.**

MATERIALS & METHODS

Equipment: 4 kW WDXRF spectrometer (S4 Pioneer, Bruker AXS).

Calibration and validation: According to ICH Guidelines. [8]

Reagents: All reagents were of high analytical grade (≥99% Reagent or Ph Eur).

Concentration ranges of calibration standards (ppm): 0-10 (Pb and Cd), 0-15 (Ir, Os, Pd, Pt, Rh and Ru), 0-25 (As and Hg), 0-30 (Cr, Mo, Ni and V) and 0-300 (Cu, Mn).

At least 6 concentration levels were considered for each element.

SAMPLES: 27 drug products (6 branded, 21 generic) and 25 dietary supplements were monitored (Figure 1).

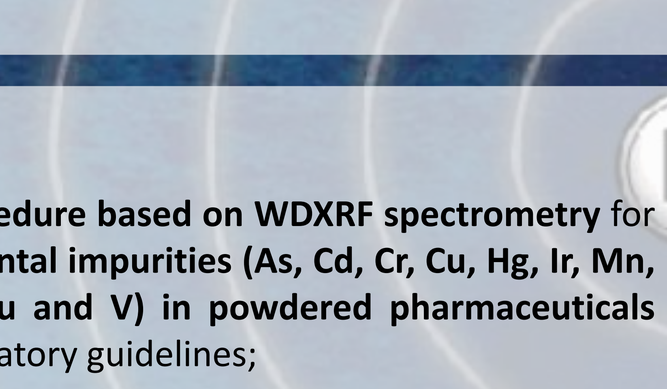

Figure 1. Sample preparation

RESULTS & DISCUSSION

In accordance with international bodies, the following validation characteristics were considered: specificity, linearity and range, limit of detection, limit of quantification, accuracy and precision (tables 2 and 3) . [8]

Table 2. Linear calibration model estimated from 21 cellulose standards

Element	Energy (keV)	Intercept/KCPs	Slope/KCps per %	r	SEE[a]
Cr	5.4	0.455 ± 0.020	406.334 ± 11.338	0.993	0.051
Cu	8.0	3.154 ± 0.216	2256.091 ± 11.789	0.999	0.522
Ir	9.2	-0.120 ± 0.026	1124.715 ± 28.960	0.994	0.066
Mn	5.9	0.030 ± 0.115	701.918 ± 6.742	0.999	0.289
Mo	17.5	-7.547 ± 0.152	4834.405 ± 84.541	0.997	0.387
Ni	7.5	0.435 ± 0.145	1782.352 ± 84.757	0.980	0.363
Os	8.9	0.507 ± 0.018	1051.716 ± 19.770	0.997	0.045
Pb	12.6	0.022 ± 0.021	1228.300 ± 38.003	0.991	0.060
Pt	9.4	0.024 ± 0.019	1114.948 ± 20.750	0.997	0.048
Ru	19.3	0.483 ± 0.007	101.636 ± 8.080	0.948	0.018
Rh	20.2	0.029 ± 0.005	63.298 ± 5.805	0.928	0.013

[a] SEE: Standard Error of the Estimate

Table 3. Limits of detection, accuracy and precision under repeatability conditions of the proposed WDXRF method

Element	LD (ppm)	Accuracy (% recovery) [a,b]	Repeatability (%RSD) [b,c]
Cr	1.62	88.0 [10]; 83.4 [15]; 84.2 [25]	1.0 [10]; 0.8 [25]; 1.1 [30]
Cu	3.16	133.5 [50]; 78.9 [100]; 77.9 [250]	1.4 [100]; 1.2 [250]; 1.8 [300]
Ir	0.76	93.9 [5]; 106.9 [10]; 88.1 [15]	9.1 [5]; 2.9 [10]; 2.1 [15]
Mn	5.41	79.1 [50]; 95.0 [100]; 74.7 [250]	1.6 [100]; 0.7 [200]; 0.9 [300]
Mo	1.04	107.7 [10]; 86.9 [25]; 86.4 [30]	1.3 [10]; 0.5 [15]; 1 [25]
Ni	2.68	82.1 [10]; 71.3 [15]; 79.6 [25]	4.5 [10]; 0.4 [25]; 1.3 [30]
Os	0.56	85.5 [5]; 68.7 [10]; 70.3 [15]	3.1 [5]; 3.6 [10]; 1.5 [15]
Pt	0.55	66.5 [5]; 79.8 [10]; 70.3 [15]	2.9 [5]; 4.3 [10]; 2.1 [15]
Ru	2.30	103.4 [10]	13.7 [10]; 16.1 [12]; 9.9 [15]
Rh	2.60	114.9 [10]	7.8 [10]; 2.4 [12]; 6.2 [15]

[a] Percent recovery of added amounts of analyte in drug samples, at 3 concentration levels, except for Ru and Rh; [b] Values in brackets expressed in ppm; [c] Relative standard deviation (%RSD) of 3 replicate measurements.

Linearity of the calibration function was excluded for As, Cd, Hg, Pd and V. The USP stringent limits for As, Cd, Hg and Pb make difficult their determination with the current analytical capacity of the WDXRF system used. For Ru and Rh (with high LQ), the minimum number of required replicated measurements was not met, which represents a limitation in view of acceptance criteria.

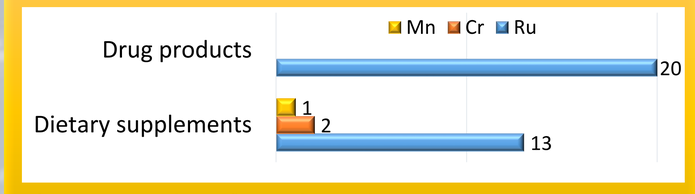

Figure 2. Number of samples with impurities above USP limits

Results obtained for **drug products and dietary supplements** may be depicted in Figure 2.

CONCLUSIONS

- **WDXRF technique may be an alternative** to the compendial recommended analytical procedures, with the **advantage of an easier and faster sample preparation,** with no dissolutions or extractions, allowing a truly **direct sample measurement**;
- The **novelty** of this work is the **application of WDXRF to final medicines consumed by the population** and not only to active pharmaceutical ingredients and/or excipients as reported so far.

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Disclosure of Interest: None Declared