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A CASE STUDY FOR RISK ASSESSMENT STUDY OF ELEMENTAL IMPURITIES IN PHARMACEUTICAL DRUGS BY INDUCTIVELY COUPLED PLASMA MASS SPECTROMETER (ICP-MS)

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ABSTRACT

Elemental impurities in drug products /substances from several sources are often observed; they may be residues or impurities from catalyst required during synthesis or from material of construction (e.g., through interactions with processing equipments or container/closure systems or by being present in components of the drug substance (Figure No.1). From January 1, 2018 a new guideline ICH Q3D, regarding elemental impurities in drug products became effective published by International Conference on Harmonization. In this article, a case study is represented by developing a selective and highly sensitive Inductive Coupled Plasma Mass Spectrometry (ICP-MS) method for the determination of Elemental impurity in Domperidone (DMP) drug substance. Determination of Cadmium, Lead, Arsenic, Mercury, Cobalt, Vanadium, Nickel, Molybdenum and Chromium content in Domperidone by Inductively Coupled Plasma Mass Spectrometer (ICP- MS) is carried out in the present work. A method is developed and study was performed to support the method precision, accuracy and Linearity. Specifically, three representative batches of drug substance Domperidone (DMP) were analyzed and the results were interpreted. The method was found suitable for the intended purpose. The linearity for all the standards was established from 30% to 150% of the concentration range (correlation coefficients were found more the 0.99). Similarly the accuracy for all the standards at 30% concentration level was estimated and recoveries were obtained in the range of 93 to 112 (%w/w). The precision of the same preparation was also found within the acceptable limit.

KEYWORDS: Risk Assessment, Elemental Impurities, Domperidone and Inductively

Coupled Plasma Mass spectrometer (ICP-MS).

INTRODUCTION

The presence of elemental impurities in pharmaceutical samples is a concern, not only because some of them are toxic, but also they may cause unwanted side-effects, or may adversely affect drug stability and shelf-life. As a result, elemental impurities must be monitored and controlled in raw materials used for drug manufacturing, intermediates, active pharmaceutical ingredients (APIs), excipients (stabilizers, fillers, binders, colors, flavors, coatings, and so forth), and in final drug products. Elemental impurities have toxicological risks to patients without providing any therapeutic benefit to the consumer. During study of some cases, it was observed that, the elemental impurities were identified in the pharmaceutical drugs[2],[3],[4],[5], which had no therapeutic benefit to the patients / human but had severe adverse effect. Based on such reported incidences, the international conference of harmonization has came up with a new guideline ICH Q3D, where in control of every element as per its toxicity has been recommended. These elements are further classified based on their toxicity and Class 1 & 2A elements, which are more toxic, needs to be controlled, either by means of risk assessment or a routine quality control check. As per ICH Q3D, for the oral route of administration, the risk assessment should evaluate the possibility for inclusion of class 1 and class 2A elemental impurities in the drug product. So we have done a case study as a risk assessment of class 1 and class 2A elements, including Mo and Cr which were considered due to possibility of their presence in the material of constructs (MOC) of equipment used for the manufacturing of drug substance, Domperidone (DMP).

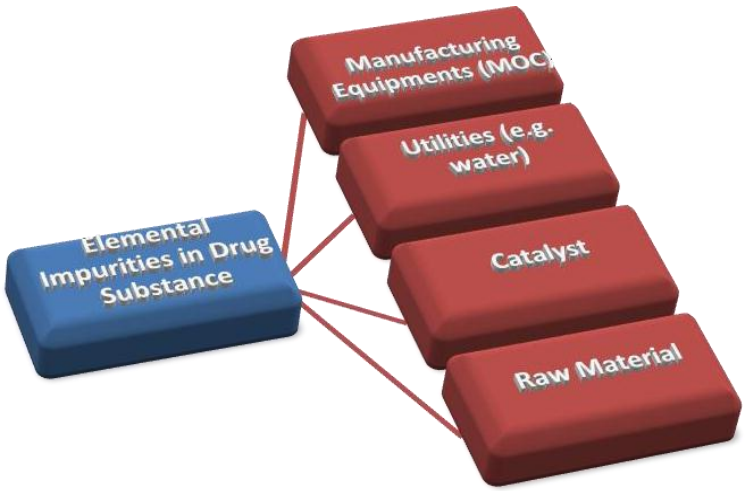


Figure.1: Sources of elemental impurities.[1]

DMP as a strong anti-emetic with minimal central effects is useful in the treatment of gastro esophageal reflux disease[6], to prevent gastrointestinal symptoms[7], treatment of nausea and vomiting.[8] The chemical name for Domperidone is 5-Chloro-1-(1-[3-(2-oxo-2, 3- dihydro-1H-benzo[d]imidazol-1-yl)propyl]piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one. Its molecular formula is C22H24ClN5O2, which corresponds to a molecular weight of 425.911 g/mol.

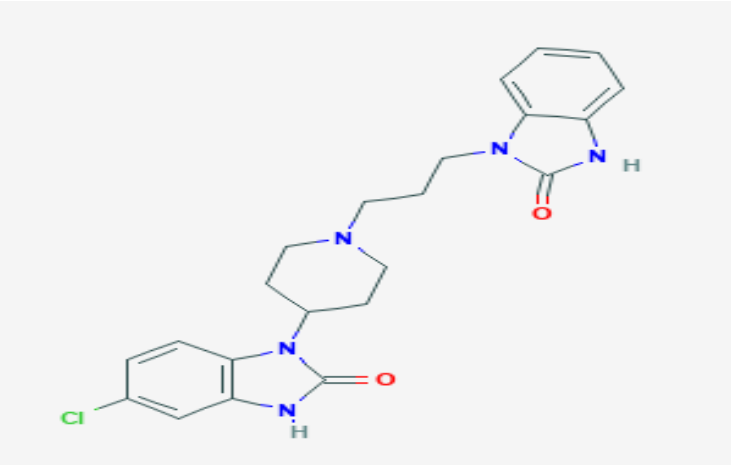


Figure.2: Structure of Domperidone (DMP).[5]

EXPERIMENTAL

Chemical and reagents

Nitric Acid (69%) was purchased from Romil while Standards stocks of required elements of 1000 ppm (ICPMS grade) were purchased from Romil and Inorganic Ventures as per the availability. Water used for the preparation of solution was from Milli-Q water purification system (Merck).

Instrumentation

ICP system is equipped with single quadruple mass spectrometer (ICP-MS Thermo (iCAP Q)) along with Q-tegra software. Microwave Reaction System of Anton paar (Multi PRO) was used for the sample digestion. Analytical balance used was of Sartorius make with model ME 235 P.

Microwave Reaction Conditions

Microwave digestion of test blank, test sample and spike test solution was carried out at microwave power of 1000W with pressure of 20 bar where Temperature range was raised uniformly up to 180°C in 15 min, kept for hold for 10 minutes and cooling was done till 50°C

in 22 minutes.

ICP-MS Conditions

The analysis was carried out in KED (Kinetic Energy Discrimination) mode at plasma power 1550W with dwell time 0.01sec with 6 No. of main runs.

Preparation of solutions

Nitric acid in water was used as a diluent for all the preparations and also taken as blank.

Linearity /Standard solution and sample preparation

Sample analysis were carried out in accordance with the requirements described in United States Pharmacopeia (USP <233> Elemental Impurities Procedures.[10-11] The linearity solutions of standard ranging from 30 to 150% of Target Limit (Refer Table No. 1) from the ready stock of 1000ppm available. Internal standardization was applied, using Yttrium (Y) as an internal standards at 1 µg·L-1 respectively.

Test samples as such and spiked test samples at 30% level (6 Preparations) was prepared of concentration as per Target limits for the 9 elements specified in ICH Q3D / USP <232> by performing microwave digestion. Filtered the solution with 0.45 u syringe filter and used the filtrate for analysis. Run the Linearity and then test solutions, spiked test solutions followed by Bracketing standards.

Table 1: Target limits for the 9 elements specified in ICH Q3D / USP <232>.

Sr. No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Elements	^{75}As	^{111}Cd	^{202}Hg	^{208}Pb	^{59}Co	^{51}V	^{60}Ni	^{52}Cr	^{95}Mo
Class	1	1	1	1	2A	2A	2A	3	3
Target limit J (µg·g-1) Limit in ppm	1.5	0.5	3	0.5	5	10	20	1100	300

RESULTS AND INTERPRETATION:

Specificity

Detection of analysis is based on Molecular weight in ICP-MS. So the instrument is highly specific for every element because every element has a different Molecular weight and detection limits. But there are chances of interference of blank with the analyte which can be controlled by blank correction to make the analysis more specific. The specificity of the method was established by observing the Interference from blank for all elements.

Interference for blank was found less than 3% of limit level for eight elements and for Lead it was less than 15%.

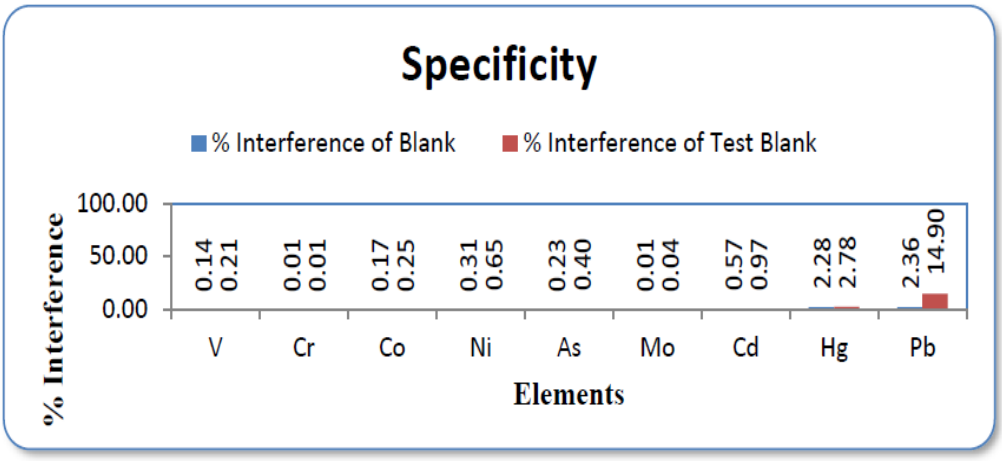
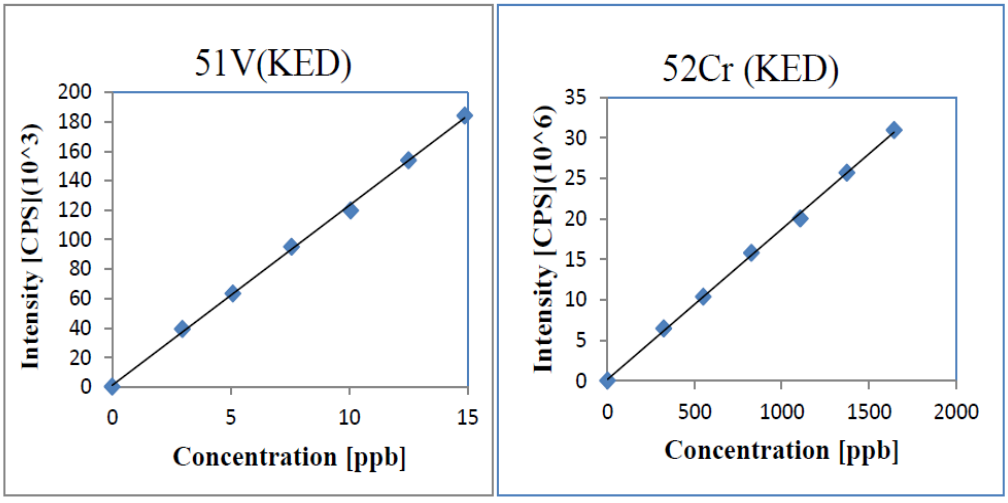


Figure 5: Interference for blank for all elements.

Linearity

Series of linearity solutions were prepared from 30% to 150% of target concentration w.r.t sample solution. Linearity curves were drawn by plotting the Intensity(CPS) against its corresponding concentration of linearity solution. Linear calibrations were obtained for all elements as shown in Figure.3. The observed correlation coefficient for linearity curve was more than 0.99 as shown in Figure.4.

Linearity lines for the target elements are shown below.



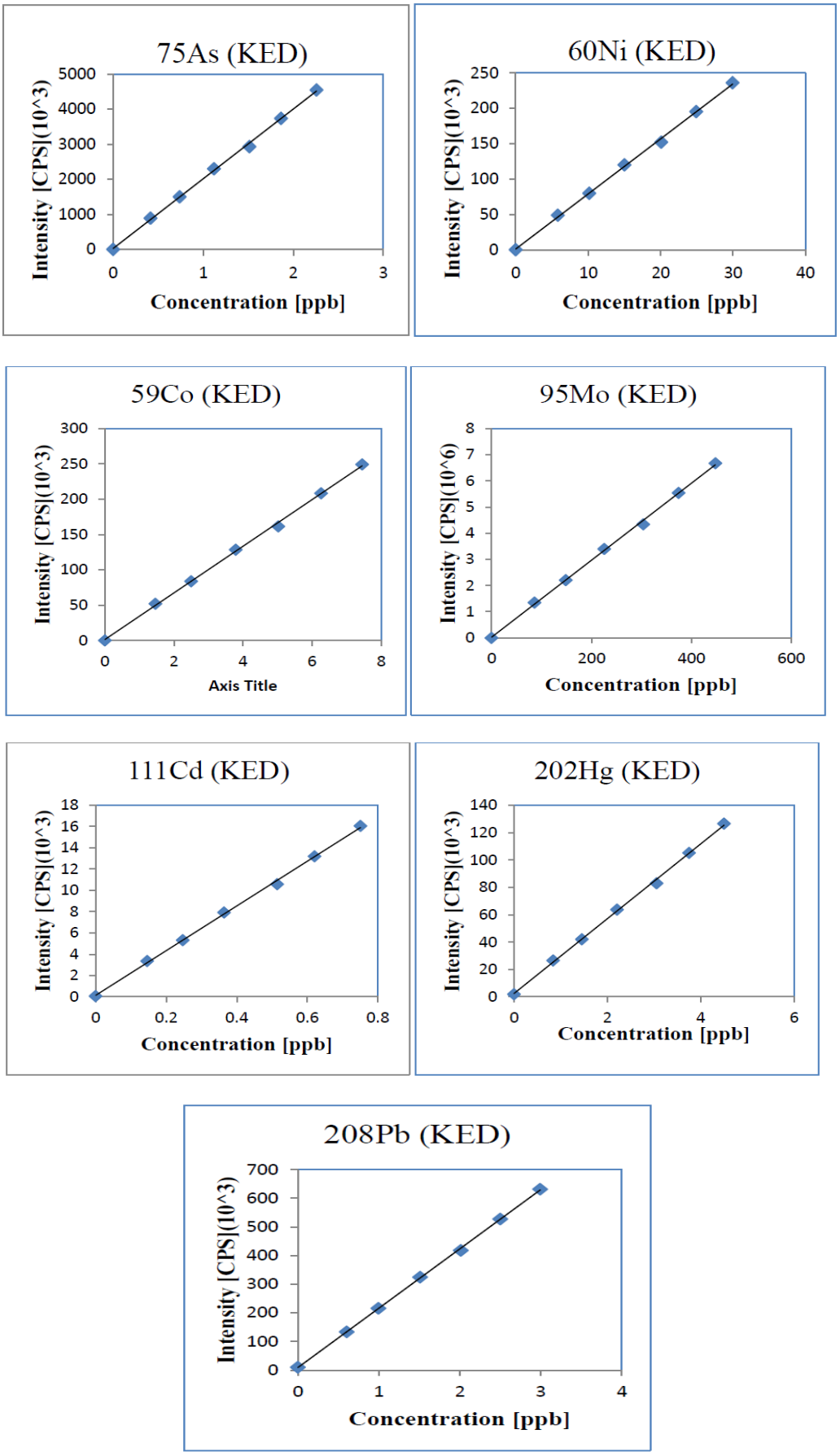


Figure 3: Linearity Curve of elemental impurities.

- Correlation coefficient:

Correlation coefficient for linearity curve is given below.

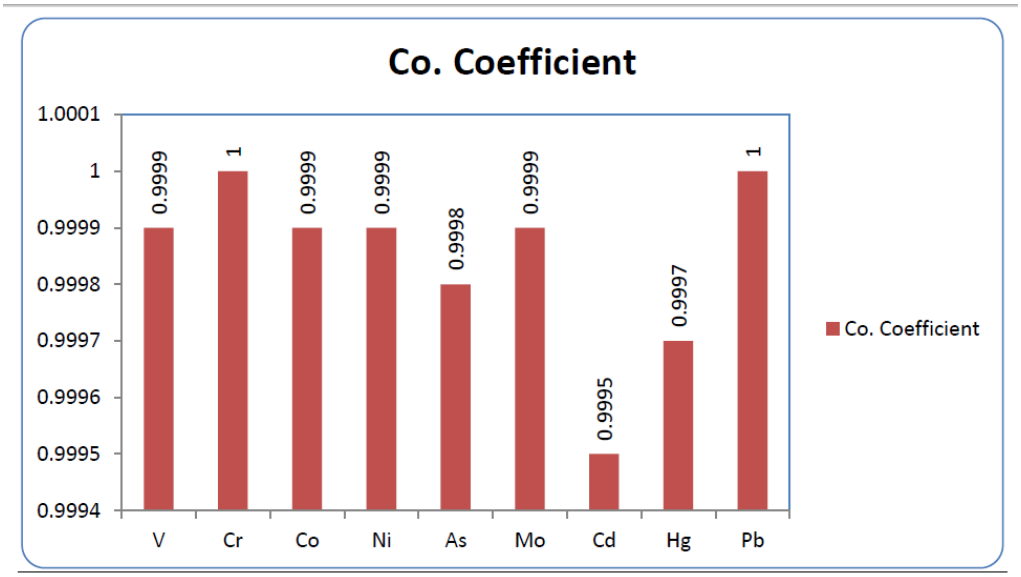


Figure.4. Correlation Coefficient for linearity Curve.

- **Drift of Intensity response of STD-6 and Bracketing standard (STD-6).**

Table No.2. Drift of Intensity response.

Elements	Observed avg. Concentration of STD 6 (ppb)	Observed average Conc. of Bracketing Std-6 (ppb)		Limit for Drift (NMT 20%)	
				Minimum	Maximum
V	14.883	15.142	14.941	11.906	17.860
Cr	1645.378	1645.288	1655.803	1316.302	1974.454
Co	7.453	7.532	7.500	5.962	8.944
Ni	29.959	29.783	30.054	23.967	35.951
As	2.259	2.231	2.337	1.807	2.711
Mo	448.461	445.364	443.650	358.769	538.153
Cd	0.751	0.759	0.735	0.601	0.901
Hg	4.504	4.451	4.393	3.603	5.405
Pb	2.992	2.968	3.007	2.394	3.590

Precision

Spike precision at 30%

Table 3: Spike Precision at 30%

Elements	V	Cr	Co	Ni	As	Mo	Cd	Hg	Pb
% RSD	1.23	0.57	0.4	0.66	3.34	0.47	2.66	1.43	0.55

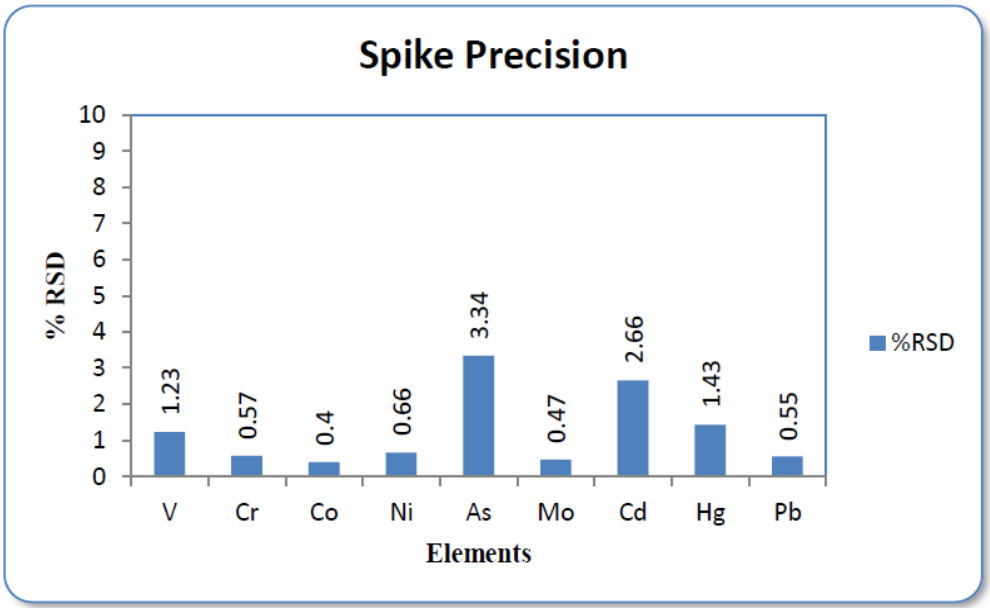


Figure 6: % RSD for 6 spike samples is well below 4%.

Spike precision was established by injecting 6 spike samples (at 30% of limit level). %RSD for spiked samples was well below 4% which show the precision.

Recovery for spike test samples, spiked at 30% of limit level (Accuracy):

The accuracy of the method was established by calculation % recovery for the spike test sample (30% of limit level) with 6 Preparations. Observed % Recovery was within 93 to 112 which is well within the acceptance as per USP.

Table 4: Accuracy.

	V	Cr	Co	Ni	As	Mo	Cd	Hg
Spiked (30%)-1	103.3	102.3	102.3	101.7	105.7	100.8	104.1	97.4
Spiked (30%)-2	101	100.8	101.8	99.9	104	99.8	96.5	94.7
Spiked (30%)-3	100.4	100.7	102.6	100	101.6	101.1	99.1	95.5
Spiked (30%)-4	99.6	101.1	101.6	101	108.5	100.3	100	93.8
Spiked (30%)-5	101.4	101.1	101.6	100.6	111.8	100.6	98.4	93.7
Spiked (30%)-6	101.5	101.3	101.9	100.6	106.7	100.1	101.7	95

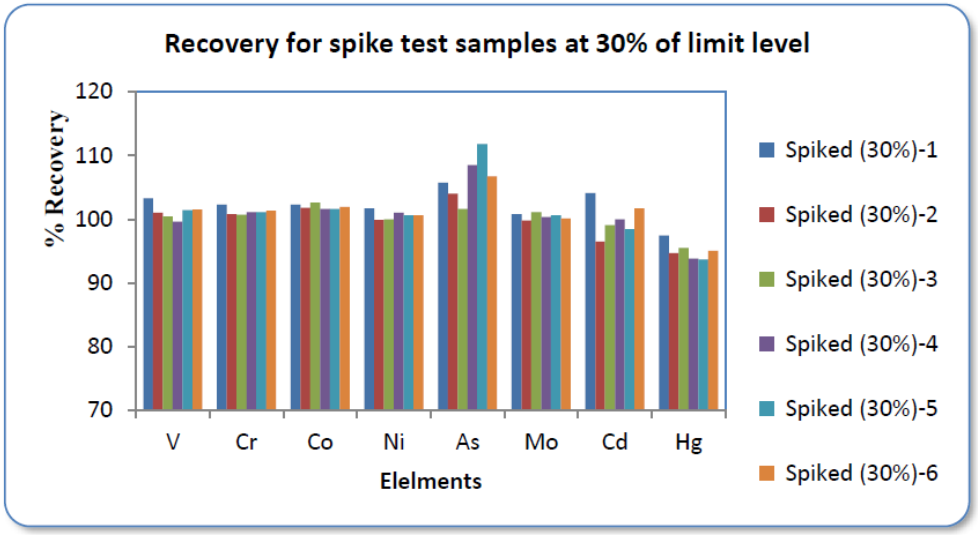


Figure 7: %Recovery for all the elements is between 93 to 112.

- **Batch Analysis**

Table 5: Batch Analysis.

Elements	Sample No.1	Sample No.2	Sample No.3
V	0.006	0.002	0.017
Cr	0.908	0.066	0.020
Co	0.005	0.001	0.002
Ni	0.012	ND	ND
As	ND	0.004	ND
Mo	0.171	ND	ND
Cd	ND	0.001	ND
Hg	0.027	ND	ND
Pb	0.002	ND	0.001

Content of all elements in batch analysis is well below 1% of limit level.

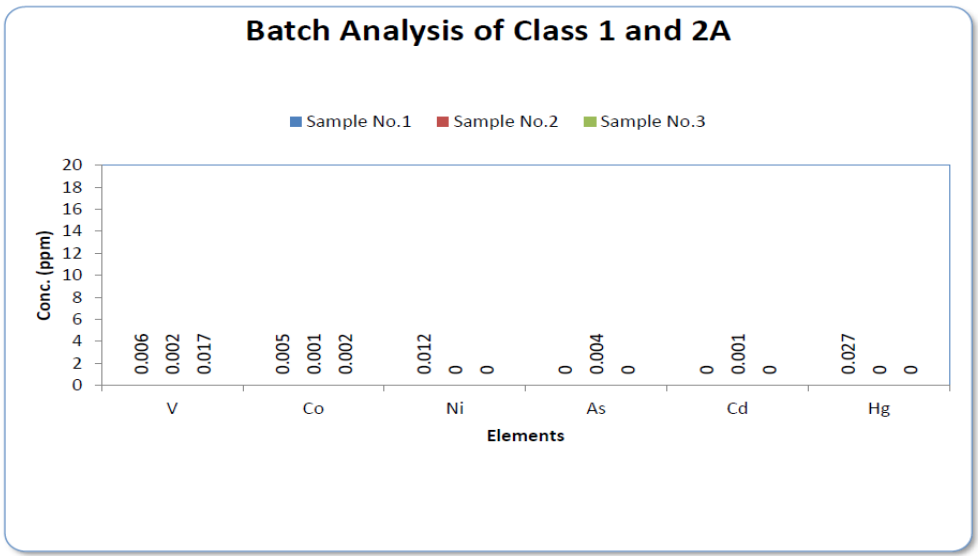


Figure.8.

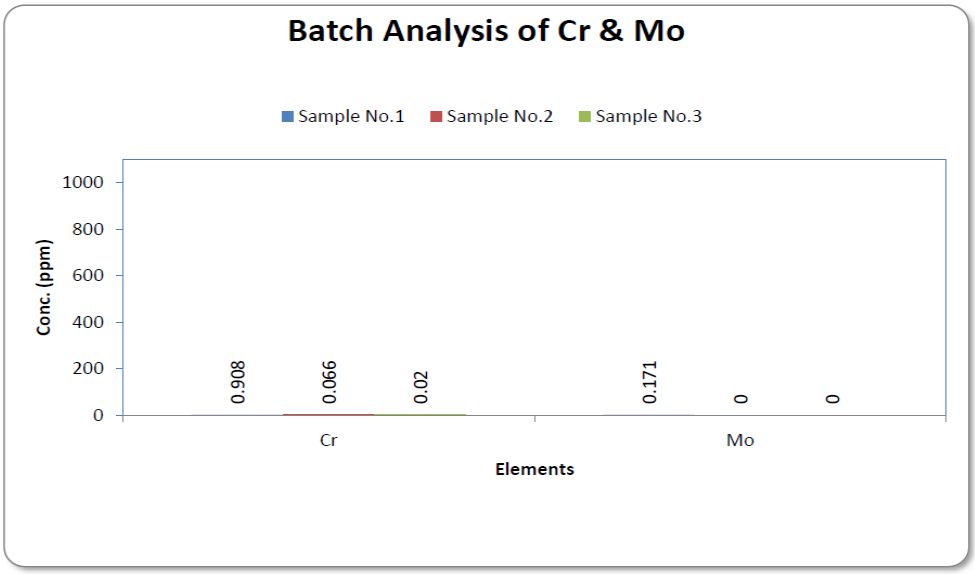


Figure 9.

CONCLUSION

If the total elemental impurity level from all sources in the drug substances is expected to be consistently less than 30% of the PDE, then additional controls are not required, provided the applicant has appropriately assessed the data and demonstrated adequate controls on elemental impurities.[9] Based on ICH Q3D, a case study for risk assessment was performed to determine the probability of presence of elemental impurities in the Domperidone and to establish the appropriate controls to ensure the quality of the drug substance.

Hence the method for determijnation of elemental impurities was developed on very selective and high sensitive technique of ICPMS. The suitability of the method was then established by; mean of Lineartiy, Specificity, Spike precision, Accuracy and Batch Analysis of Domperidone. As per USP <232> AND <233> the Linearity is to be checked from 50% to 150% of limit level. But for risk assessment approach to control elemental impurities in line with USP general chapters <232> and <233> and ICH Q3D seems workable by setting ranges from 30% to 150% of limit level as provided in this article. This also includes the exclusion criteria for routine check as proposed by European Directorate for the Quality of Medicines European(EDQM), Medicines Evaluation Agency (EMEA) or European Medicines Agency (EMA). Since the results obtained are well within the acceptable limits as per ICH Q3D, USP and even less than 30% of the PDE, hence the drug substance is safe and risk free and the routine control for elemental impurities is not required.

This is an apt case study to demonstrate the risk assessment approach, which can be employed in case of drug product / substance to comply with regulatory norms and requirements. This case can be taken as an example to decide the approach for risk assessment and elemental impurities control can be extrapolated to various products.

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