

DETERMINATION OF CATALYST RESIDUES IN ACTIVE PHARMACEUTICAL INGREDIENTS BY MEANS OF TOTAL REFLECTION X-RAY SPECTROMETRY (TXRF)

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The use of platinum group metals (PGMs) as catalysts in the synthesis of fine chemicals, pharmaceutical intermediates and active pharmaceutical ingredients (APIs) has become quite common in the last few decades. However, an unfortunate side effect of using metal catalysts is its potential to remain in the target product after isolation. For API specimens, there are typically strict guidelines to limit the levels of heavy metals based on their individual levels of safety concern. For PGMs, which are included in the Class 2 group, the concentration limit has been established at 10 mg kg⁻¹ in the API.

All pharmacopoeias include a test for heavy metals, which is commonly carried out by sulfide precipitation in a weakly acidic medium. Serious limitations of the visual heavy metals test include the lack of selectivity and the inability to detect some metals as platinum and palladium. Therefore, great effort is currently being devoted to the development of new procedures to control metals in pharmaceuticals. For instance, the United States Pharmacopoeia (USP) suggests spectroscopic techniques based on plasma (optical or coupled to mass spectrometry) as an alternative. However, the market of this type of instruments offers basically instrumentation designed for the analysis of liquid samples. Therefore, solid pharmaceutical samples have to be brought into solution in order to satisfy the need of introduction systems of most common spectroscopic techniques. Although really effective, the digestion approach is time-consuming and requires the use of corrosive and harmful reagents. For this reason, in a former work, we developed a simple and rapid X-Ray fluorescence analytical strategy for Pd determination based on the direct analysis of the solid API sample [1]. With such approach, the detection limit achieved was 0.11 mg/kg of Pd which was suitable for the intended purpose. However, the main limitation of that methodology was the amount of material needed (1g), which is unsuitable for the analysis of some expensive API samples, and also the influence of sample matrix in the quantification step.

Taking advantage of the microanalytical capability of TXRF and the lack of matrix effects due to its geometrical configuration, we have tested the possibilities of different analytical methodologies based on this technique for the determination of PGMs metals in mass-limited API samples. We compared the direct analysis of few µg of solid suspension (using different dispersant agents and sample amounts) with the analysis of dissolved and digested samples. For all used approaches, limits of detection and accuracy studies were carefully evaluated to test the real capability of the developed TXRF methodologies for the intended purpose.

The TXRF system used in this work was equipped with a W-anode tube that allowed the determination of Ru, Rh and Pd using K-lines that is not possible when employing the most commonly used Mo anode tube. Additional advantages of the low-cost compact TXRF spectrometer included the use of an air-cooled low-power X-ray tube and a Peltier cooled silicon drift detector and thus, no cooling media and gas consumption were required. These facts make this system very attractive for implementation in the pharmaceutical industrial laboratories.

References:

[1] E.Marguí, K.Van Meel, R.Van Grieken, A.Buendía, C.Fontàs, M.Hidalgo, I.Queralt. Analytical Chemistry 65 (2009)1404-1410.