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Pseudo-MRM and the Survival Yield Technique for the accurate quantification of a tryptic peptide despite isobaric co-elution

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Multiple Reaction Monitoring (MRM) is a quantification technique, usually performed in triple-quadrupole instruments (QqQ), consisting in the monitoring of intensities of at least two diagnostic fragment ions (transitions) in CID MS/MS experiments. In the context of iso-baric/meric interferences, pseudo-MRM is an alternative mode, applied for the analysis of difficult-to-fragment compounds, which relies on the monitoring, at high collision energy, of the precursor ions peak only [1]. Pseudo-MRM has shown good performances for the analysis of complex samples, due to the reduction, inside the collision cell, of isobaric co-elution. However, there is not yet a mean for determining optimal conditions for it. We propose to assess optimal conditions by using Gas Phase Collisional Purification (GPCP) [2] that relies on Energy Resolved Tandem Mass Spectrometry (ER-MS) and the Survival Yield technique. This way, optimal excitation voltage can be selected to fully fragment the iso-baric/meric interference, while keeping the analyte of interest.

Going a step further by using an internal standard (IS), the monitoring of analyte/IS ratio at several collision voltages is shown to clearly indicate the complete fragmentation of the interference with the appearance of a plateau. This is a clear and very robust indication of the total purification of the analyte. The concentration of the analyte after GPCP can then be calculated with an IS calibration curve.[3] We have applied the above-mentioned technique to quantify a tryptic peptide, at m/z 780.402, in the presence of a co-eluted isobaric interference with m/z 780.370. A triply deuterated analogue of the tryptic peptide was used as IS. This approach was applied in two cases: 1) ion trap with an unconventionally 8 m/z wide isolation window (which can be seen as a modified parallel pseudo-MRM [4]); and 2) single quadrupolar LC-MS with in-source fragmentation. In both cases, reference samples intentionally contaminated were correctly quantified despite the isobaric interference with: ~1% deviation, a linear dynamic range up to 25 µM, detection limit about 0.1 µM and a quantification limit of 0.25 µM.

References

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