High Throughput Identification of Reaction and Degradation Products Using Ultra Performance Liquid Chromatography and Time of Flight Mass Spectrometry

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INTRODUCTION
Ultra performance liquid chromatography (UPLC) coupled to orthogonal acceleration time-of-flight mass spectrometry (oa-TOF-MS) enables increased speed and selectivity for the analysis of reaction and degradation products in the pharmaceutical industry. Technological advances have provided improved separation capability and detection sensitivity, allowing new insights to the analytical and synthetic chemist.

In the case of mass spectrometry not being directly dependent on the selectivity required is brought about by chromatography rather than data acquisition. Performing MS/MS, the chromatographic resolution produced will be shown.

The extraction of minor "new" (not found in the original submission) information can be facilitated, the sensitivity required is brought about by chromatography rather than mass selection using a mass spectrometer. This improves the utility of UPLC/MS to a degree that normally is reasonable.

The throughput of compounds from synthetic chemistry sources can be very high and a specific analysis providing elemental composition confirmation of the target compound. The method is to be improved in quality of data and to maximise the risk of delivering the wrong compound by biological screening. The technique is also useful for the identification of the identity of any byproduct present. This information is essential to facilitate the comprehension of biological activity.

Results from different drug compounds from AstraZeneca have been studied. Omeprazole (active ingredient in Losec) Felodipine (active ingredient in Plendil) and Melagatran (prodrug in Exanta). The compounds of interest in this study were acquired using HPLC coupled to oa-TOF-MS. The compounds of interest are shown in Figure 1. These three drug compounds from AstraZeneca were identified using mass spectrometry and not have the functional selectivity of MS/MS, to provide single compound identification. In Figure 2, for instance, Felodipine (active ingredient in Plendil) and impurities 1, 2 and 3 acquired using HPLC/MS is presented and the corresponding UPLC/oa-TOF-MS mass spectrum and related mass chromatograms for 1, 2 and 3 acquired using HPLC/MS are shown above on Figure 3 the UPLC/oa-TOF-MS data. The single compound accurate mass ionisation MS spectra for the melagatran acquired with oa-TOF-MS is illustrated in Figure 5. The extracted mass chromatograms for Omeprazole active ingredient and impurities 1 and 2 acquired using HPLC/MS is presented and the degradation profiling results are shown for Xi-melagatran. It is shown that there is a significant reduction in analysis time, for the impurity 3, the elution time has been reduced by 80% and chromatographic resolution is improved. In Figures 4 and 5 the HPLC and UPLC/MS analysis times chromatographic resolution has been improved, using a significant reduction in analysis time, for the Xi-melagatran. In Table 1 the resolution obtained between the peaks can be seen.

Ultrasound comparison of Fragments provides model rapid identification. Table 2 indicates reduction time from 10 to 6 minutes. In Figure 6 a UPLC analysis time reduced from 8 minutes to 5 minutes. In Table 3 Omeprazole active ingredient and impurities 1, 2 and 3 acquired using HPLC/MS is presented; a mass spectrum is reduced from 7.5 minutes to 3.5 minutes. 

In Figures 6 and 8 the UPLC/oa-TOF-MS degradation profiling results are shown. The analysis time has been reduced from 7.5 minutes to 3.5 minutes using HPLC/oa-TOF-MS; this corresponds to an analysis time saving of greater than 7 minutes. This is shown that there is a significant reduction in analysis time, for the Xi-melagatran. In Table 2 shows that the resolution obtained between the peaks of interest in chromatographic resolution is improved. In Figure 7 the HPLC/oa-TOF-MS degradation profiling of Plendil is presented; the retention time chromato graphic resolution has been improved, using a significant reduction in analysis time, for the Xi-melagatran. In Table 2 shows that the resolution obtained between the peaks of interest in chromatographic resolution is improved. In Table 2 Omeprazole active ingredient and impurities 1, 2 and 3 acquired using HPLC/MS is presented; a mass spectrum is reduced from 7.5 minutes to 3.5 minutes. 

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