A Novel Approach using UPLC-ToF MS^E and the UNIFI Scientific Information System to Facilitate Impurity Profiling of Pharmaceuticals

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INTRODUCTION

Impurity profiling of the active pharmaceutical ingredient (API) is an essential part of drug development. It is critical to ensure safety and quality of the API—and the resultant drug product, and enables a more thorough understanding and better control of the synthetic process. By monitoring and characterizing degradation pathways, impurity profiling gives insight into the impact of storage conditions.[1,2]

Recently, the development of ntelligent software tools such as the UNIFI Scientific Information System has proven extremely beneficial to scientists for data evaluation, interrogation, and storage of information in libraries. It also represents a powerful analytical platform for HRMS impurity profiling.

Aripiprazole was subjected to accelerated stress conditions to generate degradation products A comprehensive precursor and product ion dataset was acquired by use of the MS^E acquisition mode.

The resulting impurities were identified and easily visualized using the UNIFI Scientific Information System. In addition, data for characterised impurities could be saved to the Scientific Library and utilized for future screening under differing degradation or synthetic conditions.

METHODS

Experimental

Base and temperature degradation: The base-catalyzed and temperature degradation studies were carried out by adding a small aliquot of 0.1 mM ammonium hydroxide to an aqueous solution of aripiprazole. The sample was then left at 80 °C and aliquots were taken at 0-, 6-, 24-, 48-, 72-, and 96-hour time points. The samples were diluted 1 in 10 with mobile phase prior to injection.

Oxidative degradation: The oxidative degradation was performed by adding 30% H_2O_2 to an aqueous solution of aripiprazole. Samples were diluted 1 in 10 with mobile phase prior to injection.

LC/MS Conditions

Column: ACQUITY BEH C18 1.7 µm, 2.1 x 150 mm

Mobile phase A and B: water and acetonitrile both with + 0.1 % formic acid

Gradient: 5% to 60% B over 7 min, up to 100% for a further min, equilibrate for 2 min. Total time 10 min.

Flow rate: 0.4 mL/min

Instrument: Xevo G2-XS operated in ES positive ion mode
Acquisition rate: 0.1 scan/sec

MS^E Method: Low energy 4 eV, high energy 25-45 eV

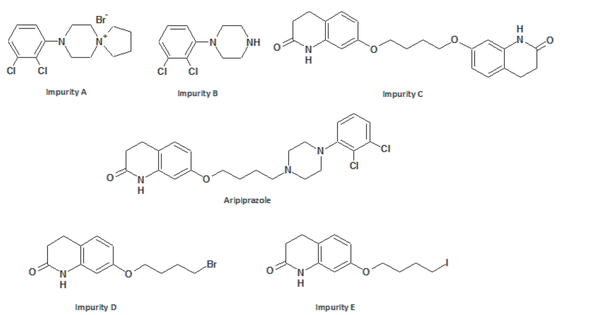

Fig. 1: *Shown are several known degradation products of aripiprazole which were added to the Scientific Library within UNIFI.*[3]

Fig. 2: *An example impurity identification workflow within UNIFI. The selected Impurity Review step shows an overview of the impurities identified in the Component Summary. The extracted ion chromatogram and spectra are also shown are the component highlighted.*

RESULTS

The UNIFI Scientific Information System allows a series of workflow steps to be created that are designed to enable visualization of the entire dataset so that the information required to make a decision can be easily accessed. This approach facilitates consistent, concise, and rapid review of an entire sample injection series within an analysis. These steps can be customized and created to suit a particular analysis. An example of a workflow designed for impurity identification data review is shown in Figures 2-7. Figure 2 illustrates the 'Impurity Review' step within the workflow, with chromatographic and spectral data shown.

The Scientific Library within UNIFI is an integral part of the software package and is used as a repository for storing information as well as structures. Impurity identification within UNFI begins by storing the structure of the API in the scientific library. The possible degradation products of the API can then be generated and searched for during automated processing. The structure information is also used to automatically annotate product spectra.

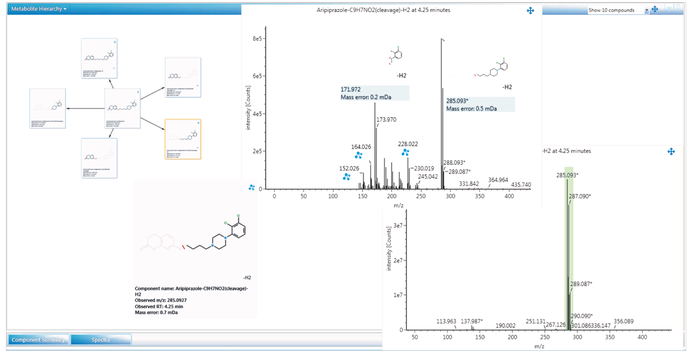

Fig. 3: *The impurity hierarchy map is a visual representation with the API at the centre and the identified impurities surrounding it. Low and high energy MS^E spectra can also be displayed.*

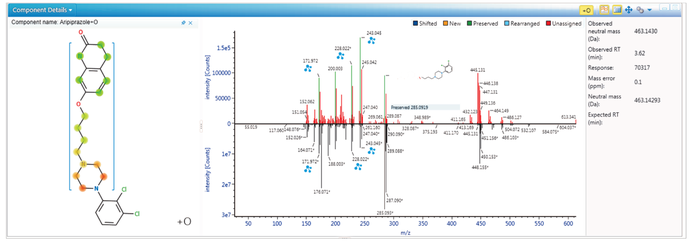

Fig. 4: *Automated transformation localisation. The MS^E spectrum of the impurity aripiprazole+O (Top) is shown with the inverted MS^E spectrum of aripiprazole (bottom).*

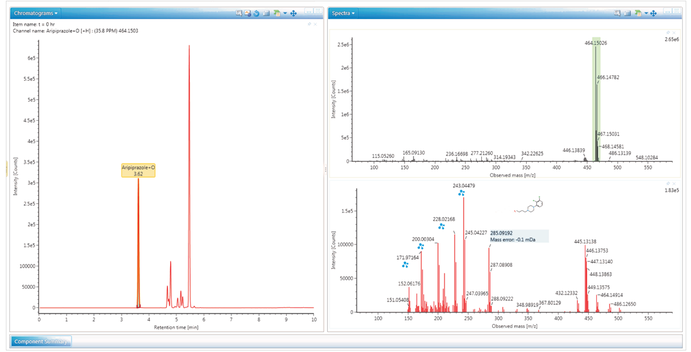

Fig. 5: *Oxidative degradation of aripiprazole forming several oxidative impurities. The XIC and low and high energy MS^E spectra are shown for the hydroxylated impurity at 3.62 minutes.*

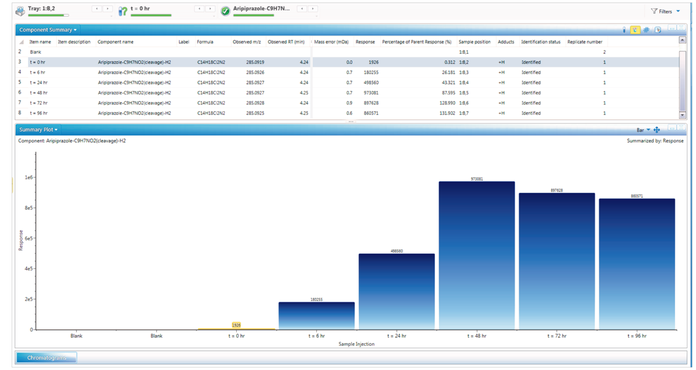

Fig. 6: *Summary plot view of the increase in the major impurity at m/z 281.09 over the time course experiment as aripiprazole degrades.*

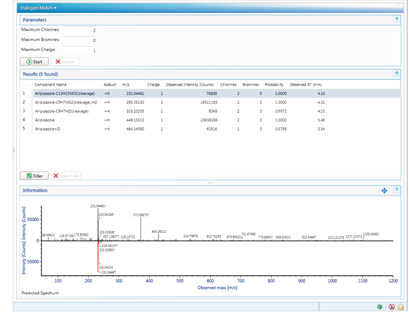

Fig. 7: *Halogen matching within the elucidation toolset set to search for an isotopic pattern indicative of a maximum of two chlorine atoms.*

CONCLUSIONS

Impurity identification of aripiprazole in forced degradation experiments was successfully completed using ultra performance liquid chromatography, high resolution mass spectrometry, and the UNIFI Scientific Information System. The ability to acquire accurate MS^E data within one injection gave a complete overview of the samples and allowed aripiprazole and its impurities to be identified. UNIFI enabled the use of customizable workflow steps to allow data analysis to be performed easily and efficiently. The relationships between aripiprazole and its impurities were easily visualized using the data evaluation tools present in UNIFI.

The Xevo G2-XS is a highly sensitive HRMS platform with high mass accuracy compatibilities. These capabilities enable rapid and confident detection of impurities and confirmation versus a targeted approach through pre-defined library entries.

REFERENCES

1. MD Jones and RS Plumb. "The application of sub 2-µm particle liquid chromatography operated high mobile linear velocities coupled to orthogonal accelerated time-of-flight mass spectrometry for the analysis of ranitidine and its impurities." *Journal of Separation Science*. 29: 2409-2420; 2006.
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