Development of LC-MS Extractables and Leachables System Suitability Standard Mixture for Screening

RESOLIAN
ANALYTICAL SCIENCES

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Introduction

Leachables that are present in packaged drug products or released from medical devices can adversely affect patient health and safety. This is why it is important for routine screening of packaged drug products to be conducted for unspecified leachables, and packaging system or medical device extracts to be screened for unspecified extractables as potential leachables, a process known as non-targeted analysis (NTA).

For qualified methods utilised during extractables and leachables studies, system suitability testing is conducted during each chromatographic run to ensure that the method performs properly at the time of use. System suitability testing in extractables and leachables screening requires a standard mixture of relevant compounds that are commonly observed as extractables or leachables. For the development of a system suitability standard for use in Resolian, the approach recommended by the United States Pharmacopeia (USP) was used to select a range of candidate analytes that represent a population of structurally, functionally, and chemically diverse compounds that are deemed likely to be observed by ESI and APCI using ultra-performance liquid chromatography and high-resolution accurate mass spectrometry (UPLC-HRAMS).

USP Member categories

The mixture satisfies the following requirements:

A) Anchor compounds:
Earliest and latest eluting compounds, establishing the chromatographic breadth of the method.

B) Critical pair:
Closely eluting compounds to establish the method's chromatographic efficiency and resolving power.

C) Sensitivity compounds:
Candidates that establish that the method is sufficiently sensitive for its purpose.

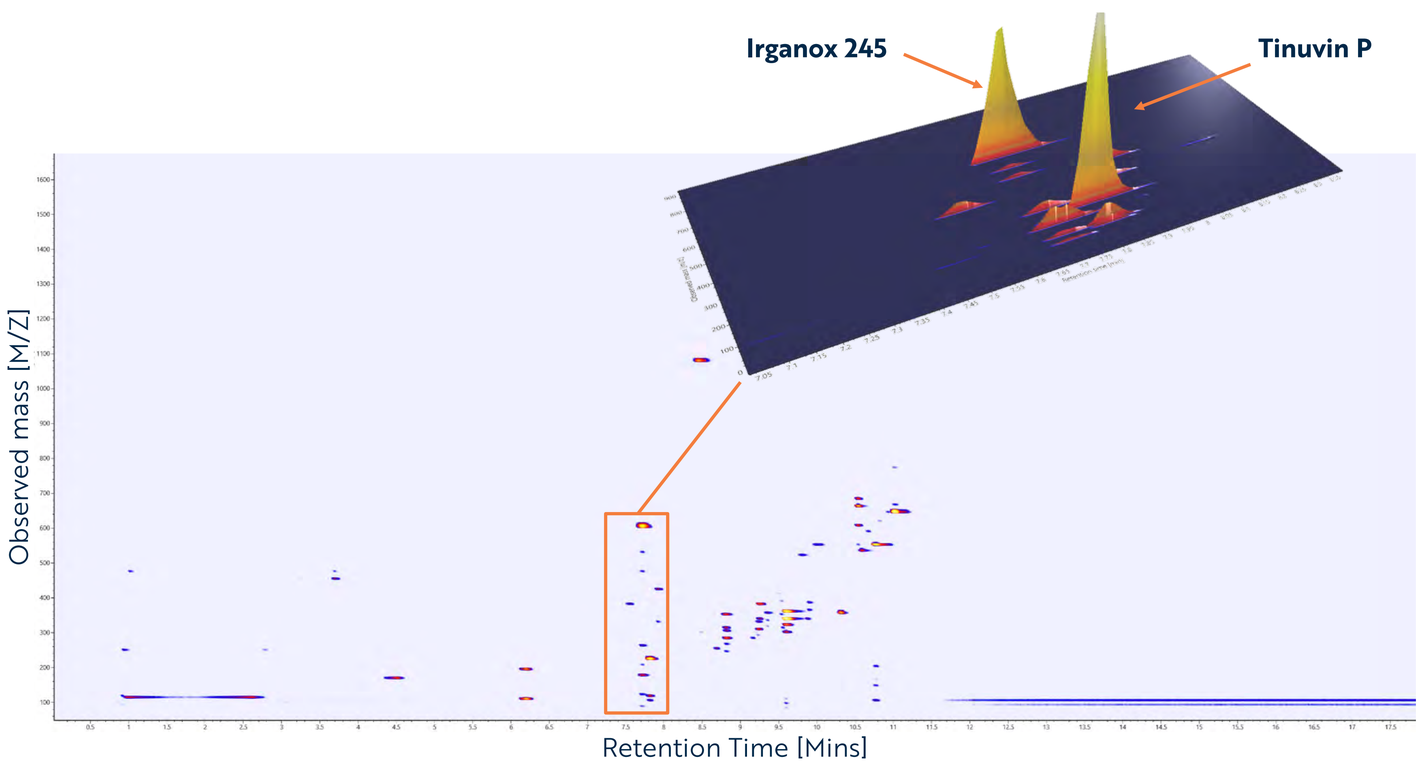
D) Overlapping compounds:
Candidates detectable by the method in question and a second screening method.

E) Precision compounds:
Candidates that elute throughout the chromatogram to establish the method's injection precision.

F) Compounds to add chemical diversity:
Present in the mixture to ensure that the mixture contains chemically diverse members.

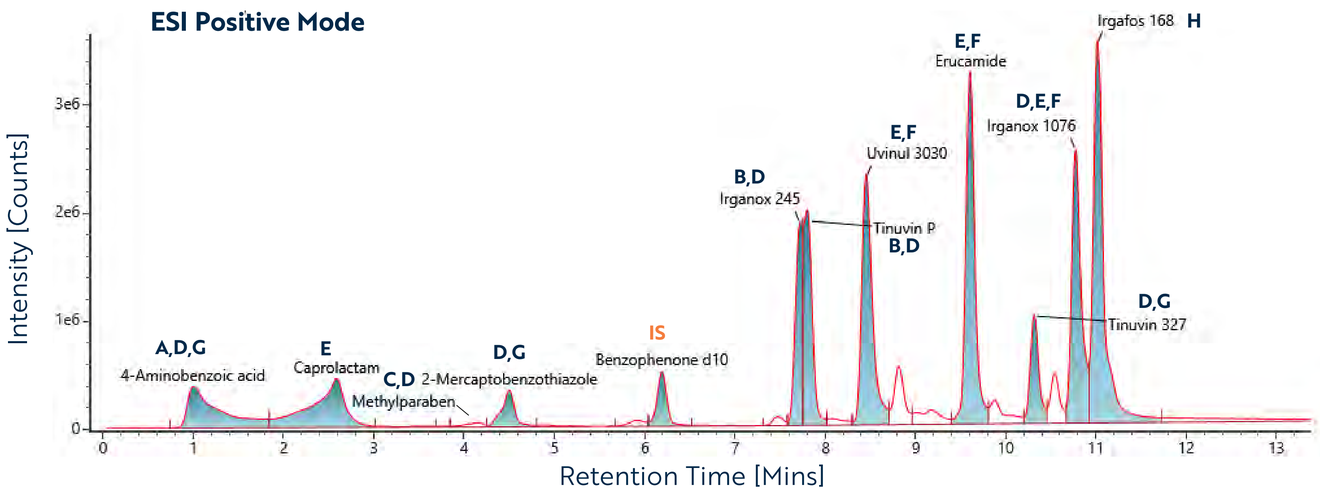
G) Compounds of potentially toxic substances:
Candidates whose presence in a test sample could pose a potential toxicological safety risk.

3D Extracted Ion Spectrum



With the aid of 3D peak detection algorithms, co-eluting compounds with an overlapping retention time can be separated by their accurate m/z value, further improving the effective selectivity and peak capacity of the methodology.

Total Ion Chromatogram



- Each member of the standard mixture performs one or more relevant functions.
- The compounds in the reference mixture represent differing functionalities and chemical properties.
- Overlapping compounds are also detectable by ESI negative mode or APCI positive mode, or both techniques.

Summary

- ✓ A standard mixture was developed incorporating the principles of the proposed United States Pharmacopeia (USP) approach.
- ✓ Each compound in the standard mixture has a specific, justified purpose for being in the mixture based on their physiochemical properties or interactions with the methodology.
- ✓ The use of recognized Extractable and Leachable compounds within a system suitability mix gives confidence that the UPLC-HRAMS method is suited for its purpose.

References

- United States Pharmacopeia (49-4). Stimuli PF, Proposals for the Development -, Composition, and Routine Use of System Suitability Standard Mixtures in Support of Chromatographic Screening for Organic Extractables and Leachables. STIMULI PF. Rockville, MD: United States Pharmacopeia.
- DOI: https://doi.org/10.31003/USPNF_S203084_10101_01

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