Conclusion

Advanced mass spectrometric applications for performing qualitative and quantitative analysis of small molecules are of great interest over the last years. The combination of high sensitivity and selectivity, which are requested by official bodies, has driven this information-rich technology to an essential tool in pharma analysis. The variations and permutation combinations of different ionisation techniques with the different analysers provide the analysis of divers chemical entities at the femtogram level.

HWI provides a variety of MS instruments to fulfil the requirements in regulated GMP environment, such as quadrupole, triple quadrupole (QQQ) and quadrupole time-of-flight (QToF) mass analysers coupled to LC and GC systems.
As powerful ionization techniques EI (coupled to GC), ESI and APCI (coupled to UHPLC) are available sources. Our experts are developing appropriate methods for each type of molecule and question to provide a full quality assessment of your pharmaceutical compounds and products.

HWI mass spectrometric equipment

- (HS)-GC-MS (EI)
- UHPLC-UV-MS/QQQ (ESI, APCI)
- UHPLC-UV-MS/QTOF (ESI, APCI)
- LC-UV-SPE (for isolation)
- ICP-MS (available with partners)

Contact

We are pleased to personally discuss your current questions and looking forward to our collaboration!

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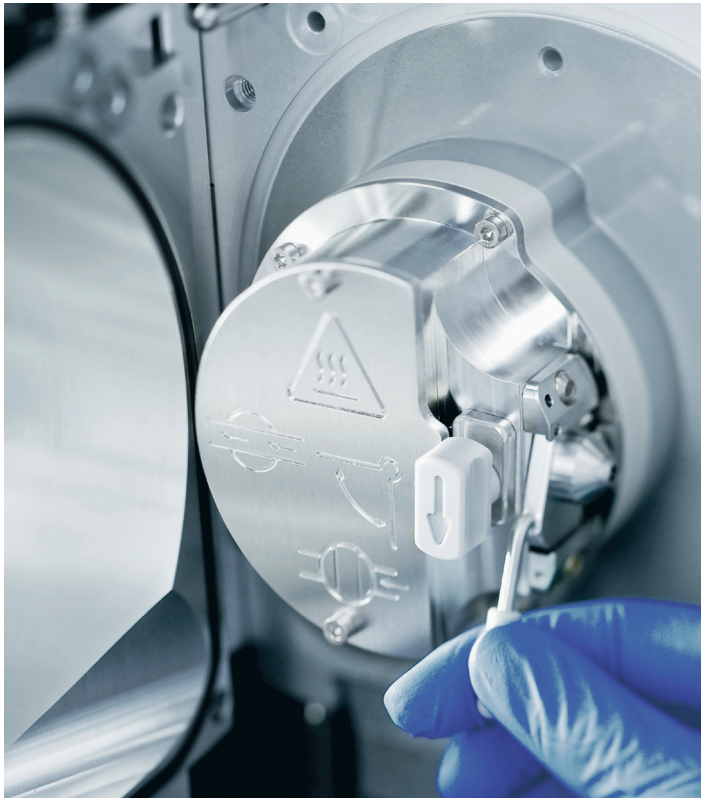

Mass Spectrometric Services

your success is our success

HWI group

Mass spectrometric applications in pharmaceutical quality control

Mass spectrometry (MS) technology has evolved to the point where it is used throughout the drug development process, and now plays a key role in advancing the production of pharmaceuticals and the quality control thereof. In particular, when MS is coupled with a chromatographic separation technology (such as HPLC-MS and GC-MS), it becomes a powerful analytical tool, which adds an orthogonal detection function to the common UV detection for sample analysis, and provides information-rich assessment of pharmaceutical compounds.
Many active pharmaceutical ingredients (APIs) become increasingly potent and stringent regulatory requirements both call for highly sensitive methods providing full profiles of drug and impurities. MS technology has evolved to meet this need and is emerging as the tool of choice for many applications in such complex pharmaceutical analyses.
Using MS in quality control and GMP environment, HWI offers impurity identification and profiling, quantitative analyses of potential genotoxic impurities (PGIs), cleaning verification/validation (CV) as well as extractables/leachables studies (E&L).

Impurity identification and profiling

Impurities in drug substances (APIs) are synthetic by-products, starting materials, intermediates, etc., while in case of drug products these constitute degradation products formed on storage. Toxic impurities, regardless of source, are of particular concern during safety evaluation, process research activities and during dosage form development, because of the rigorous regulatory requirements outlined by various international agencies. The common strategy for purity determination is the usage of (U)HPLC chromatography coupled with a diode array detector. HWI provides mass fingerprinting techniques, like LC-UV-MS/QTOF, LC-UV-MS/QQQ, which have proven to be very useful for online characterisation and structure elucidation of impurities also in trace concentrations as orthogonal detection function to the common UV analysis. One challenge in elucidating the structure of unknown compounds using MS is that non-volatile buffers (like phosphate buffers, ion-pairing reagents, etc.) are not amenable to MS ionisation. Often method adaptation to MS compatible conditions is required. Where this is not feasible, two dimensional (2D)-LC-MS and fraction collection can be used to overcome this issue and has the added advantage of improved chromatographic resolution. For an unambiguous identification, preparative solid-phase extraction via our automated LC-UV-SPE fraction trapping system is employed for specific isolation with subsequent multidimensional NMR analyses. Structure confirmation often includes a synthetic approach.
HWI offers a full qualification of the synthetic substance as reference standard. In case of volatile compounds, a coupled system of (HS)-GC-MS and comparison to convenient databases (commercial and in-house libraries) helps in rapid identification for a full impurity profiling of pharmaceutical products.

Stability studies of drug substances and drug formulations

During the development phase, drug substances as well as drug formulations are subjected to stress testing under a variety of stress conditions, such as temperature, humidity, acidity, basicity, oxidation, light, etc. The same facilitates validated analytical method development and provides extrapolative information for upcoming formulation and packaging studies. For these studies, practical approaches to attain structural elucidation of degradation products using modern LC-MS or LC-MS/MS techniques and information obtained from them, such as retention time, molecular weight and fragmentation pattern, has gained paramount importance. The strategy for identification of degradation products during early development requires fast and sensitive LC-MS analytical methods. These techniques are also extended later during the analyses of long term as well as accelerated study stability samples to obtain useful and relevant information.

Quantitative analyses of potential genotoxic impurities (PGIs) and cleaning validation studies (CV)

For exact quantitation, e.g. for potential genotoxic impurities (PGIs), triple-quadrupole (QQQ) LC MS systems are prevalent as they can detect multiple impurities simultaneously well below the limits required by regulatory authorities by using LC-MS/MS in MRM mode.
Although LC-MS/MS has long been recognized as a state-of-art, high-sensitivity tool for quantitation, LC-HRMS is showing promise, particularly where efficiency and fit-for-purpose quality are critical. In full scan HRMS experiments for small molecule quantification, selectivity can be achieved by creation of extracted ion chromatograms (EIC) of the compound of interest, with a narrow mass-extraction window. This can be a good alternative to the common QQQ-MS analyses. Having both MS systems in house, HWI provides the technique for quantitation, appropriate to the question of our customers.
Cleaning verification (CV) also demands highly sensitive analytical methods. LC-MS/MS is well established as a versatile tool for quantifying known compounds in the solvent rinsates or swabbing extracts from manufacturing equipment. This is especially useful when dealing with cleanout testing for high potency drugs, where the acceptance criteria require low ng/mL detection.

Extractables/Leachables studies (E&L)

Although drug containers and modern drug delivery systems meant to protect a drug from environmental contaminations, they might be themselves a source of contamination. The detection of extremely low levels of extractables and leachables in large-volume parenteral formulations, for example, is challenging the limits of conventional analytical techniques and is replaced by modern mass spectrometric applications. Using highly sensitive in-house MS screening methods, especially developed for the detection of impurities from containers and closure systems, HWI offers comprehensive analytical workflows for the analysis of extracts and product formulations including LC-UV-HRMS and (HS)-GC-MS for confident identification and quantification of organic contaminants.
Elemental impurities are determined via inductively coupled plasma mass spectrometry (ICP-MS), which is the technique of choice for accurate elemental determination in pharmaceuticals as well as in analysing leachables of e.g. closures and containers. It offers many advantages including small sample size, element specific information and rapid sample throughput and is the endorsed technique via United States Pharmacopeia (USP) for identifying and quantifying elemental impurities.
HWI offers the complete E&L portfolio including tailored concepts for extractables studies with the packaging material, leachable screening using the drug product as well as (if needed) leachable studies and routine testing.