Enhanced separation in ambient mass spectrometry imaging

Valorization

The research presented in this thesis focusses on innovative technological developments in quantitative ambient mass spectrometry imaging (MSI) for the pharmaceutical industry. There is a high demand for robust and validated imaging tools in the pharmaceutical pipeline. Over the last decade, MSI has established itself as one of those imaging tools that can distinguish between drug candidate and its metabolites. Early implementation of MSI in pre-clinical drug discovery and development (pharmacology) can prevent costly investments in potential drugs that proved not effective in the clinical phases. The impact of MSI on the pharmaceutical pipeline is indispensable which explains the broad interest from major pharmaceutical companies. Janssen Pharmaceutica (Janssen R&D in Beerse, Belgium) has expressed interest in applying MSI workflows in their laboratories alongside the existing LC-MS analyses. The collaborative research program between Janssen R&D and the Maastricht MultiModal Molecular Imaging (M4I) Institute was established in 2015. Janssen R&D not only provided funding but even more important supported this research program with drug candidates, tissue samples, and valuable expertise. Together with Janssen R&D, new research ideas were initiated, developed, and applied to their samples. Not surprisingly, the research presented in this thesis has led to the application of these new techniques and products that are directly translatable to their drug development process. The close collaboration did not only lead to sharing new techniques/products but also to knowledge transfer. In 2015, MSI was hardly known and pursued within Janssen R&D. Now five years later it has become an established technique, which is being used more and more in various parts of the drug discovery and development pipeline, and in a variety of therapeutic areas, like neuroscience, infectious diseases, oncology, etc. The research value of these techniques and products have been addressed in the individual thesis chapters. Here, we will briefly describe the commercial and economic impact of this research for Janssen R&D and other commercial collaborators.

Spatial LC-MS analysis

The collaboration between Janssen R&D and M4I started with a project to bridge LC-MS with MSI and resulted in the development of the HR-LESA-µLC-IMS-MS^E platform (**Chapter 2**). This platform was established together with our commercial partners from Advion (TriVersa NanoMate) and Waters Corporation (Acquity UPLC® and Synapt G2-Si). The use of the TriVersa NanoMate as a spatial sampler and an LC autosampler in one is since our research publication sold by Advion as an additional TriVersa NanoMate module known as $LESA^{plus}$. This allows already existing LC-MS methods to be upgraded with a spatial sampler to add invaluable spatial information to the analysis.

Q-MSI in pharmaceutical development

The 3D printed mold for the preparation of a mimetic tissue model is a perfect example of how a collaborative environment leads to innovative ideas. After discussing a revised mimetic tissue model (Barry et al.), Darya Hadavi (a fellow M4I colleague) suggested to use a 3D printed mold for the preparation of a gelatin block. A brainstorm session resulted in a new design for a first prototype which was immediately tested in the M4I laboratory. After the prototype was optimized to the final version, Janssen requested a few extra copies to be used in their laboratory. This is the version that was used in the research reported in Chapter 5 and depicted in Figure 7.1.

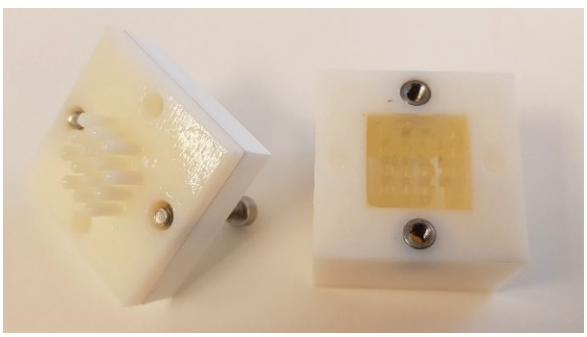

Figure 7.1 An image of the 3D printed mold that is implemented in an efficient Q-MSI workflow

MRM based imaging

At the M4I institute, the newest state-of-the-art mass spectrometers are available. This has been expressed by the introduction of M4I in the Waters Center of Innovation. Waters Corporation has been a key player on the market with innovative new MS instruments, amongst other fast high throughput triple quadrupole (QqQ) instruments. The purchase of the DESI source from Prosolia proved that their interest is becoming a major provider of ambient imaging tools. The close collaboration between Waters Corporation, M4I, and Janssen R&D resulted in the investigation of DESI-MRM imaging and the analytical comparison of this technique with other DESI-MSI instruments/modes as presented in Chapter 4 and 5. The setup of DESI-QqQ in the M4I laboratory is represented in Figure 7.2. The ability of performing dual polarity experiments on a QqQ instrument saves an enormous amount of time and money when two experiments can be merged into one. Shortening analysis time for known compounds in large scale drug studies with reliable instruments is in the advantage of every academic and industrial scientist.

Figure 7.2 Desorption electrospray ionization source mounted onto a triple quadrupole mass spectrometer

After the multiplatform presented in **Chapter 5**, we believe that MRM based imaging for the pharmaceutical industry should become the standard mode of operation due to its improved analytical performance. In line with this statement, we should refer to the MALDI-QqQ instrument, Flashquant™, manufactured by Applied Biosystems in 2007 which has been taken off the market shortly after its release. One could conclude that the academic and industrial interest in MRM imaging is not significant. In 2007, the MSI field was 'only' 10 years old and very much in a developmental stage in where new imaging ion sources and MS instruments were commercialized. The investigation of applied MSI became much later. We assume that in 2007 insignificant fundamental research showed the benefit of MRM imaging leading to not enough interest in an instrument suitable for standardized routine analysis. Nowadays, MSI is much more focused on its application and is in our opinion ready for sensitive and reliable pharmaceutical MRM imaging applications that will continue to add value from fundamental and methodological research.