LC/MS Applications in Drug Development

By Mike S. Lee, John Wiley & Sons, 2002, €105.90, 243 pages in hardback, ISBN 0-471-40520-5

Mass spectrometry has become one of the enabling technologies in pharmaceutical research and drug development because MS, and especially LC–MS, meet many of the demands of drug development, such as sensitivity, selectivity, speed and cost effectiveness.

Lee gives a clear and detailed overview of the drug development process. He explains how a chemical compound evolves and reaches the market as a new drug approved by the authorities. In the drug discovery process new chemical entities are tested first for activity. Development candidates are then formulated as a drug product that can be tested in humans in the clinical phases to show efficacy and safety and, eventually, receive marketing approval. As attrition rates in drug discovery are high, only one in many thousands of lead compounds might come to market.

The author explains instructively how LC–MS can help in a quantitative and qualitative manner to accelerate development times and save costs by helping to choose the right candidates much earlier.

In a regrettably short chapter (*LC/MS Development*, Ch. 4), Lee describes the history of LC–MS coupling from historical to modern interfaces. For the reader, however, it remains unclear as to what made the revolutionary difference that started the LC–MS boom. The author should have explained that the main difficulty of historical LC–MS coupling was the high gas load resulting from eluent evaporation and the detrimental consequences for the high vacuum of the mass spectrometer. It was only atmospheric pressure ionization (API) interfaces that circumvented these difficulties by applying an ionization process outside the vacuum system at atmospheric pressure. This was the real quantum leap in LC–MS that enabled for the first time a rugged and easy interface.

The longest chapter of the book, *LC/MS Applications* (Ch. 6), deals with the vast field of applications in R&D and profits from the author's considerable experience in the pharmaceutical industry. He describes in detail possible uses of LC–MS, such as combinatorial library screening, high-throughput and proteomics applications in pharmaceutical research. Examples in drug development include pharmacokinetic quantification where LC–MS first entered the pharmaceutical world in the late 1980s. For this kind of analysis, LC–MS has become, and still is, the gold standard. Another strength of LC–MS is the identification of metabolites, impurities or degradants.

More importance should have been given to the advent of high-resolution accurate mass measurements, which was quite a second quantum leap for LC–MS. The ability to determine masses with an accuracy of a few ppm offers the possibility of assigning elemental formulas in the structure elucidation of impurities. For proteomics, the possibility of performing database searches with accurate masses results in much shorter hit lists, thus giving more confident results.

Readers unfamiliar with LC–MS will be given many examples and ideas of how LC–MS can help in the development of new drugs but they will not always understand the often detailed cases described. The overwhelming information given on applications contrasts with the sparse information given on the technique itself; a glossary is not sufficient.

It is a shortcoming of the book to concentrate only on applications and to neglect the fundamentals. Without this knowledge, an inexperienced reader can not judge the potential and real capabilities of LC–MS and could think of it as being just as easy as LC–UV, albeit with a higher information content. This perception would be misleading; LC–MS is not a panacea. The crucial step is ionization, which is still far from universal. Therefore, new interfaces must be developed if electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) fail as in the case of, for example, the new atmospheric pressure photo ionization (APPI) interface. Other drawbacks of LC–MS, such as the restriction to volatile buffers, are never discussed nor is the fact that for every application the choice of the interface and ion polarity is crucial.

There are not many books available on LC–MS and a work on its applications in drug development has long been awaited. It is consequently a pity that the author too often adopts a management view in preference to instructing the reader on LC–MS fundamentals. This book is therefore only a valuable introduction for someone entering the field of pharmaceutical development who is already experienced in this technology.

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