High-throughput purification: walk-up versus dedicated support

'The challenge is high productivity and quality – chemists need the right level of support to achieve this important goal.'

Mark Jones, Director, Combipure

Combichem – living up to expectations?

The impact of combinatorial chemistry within the drug discovery world might not have lived up to earlier expectations. However, many important lessons have been learned *en route* and chemists have been introduced, for the first time, to the concept (and culture) of automated high-throughput synthetic techniques. The introduction of combinatorial chemistry, in the early 1990s, resulted in the rapid expansion of company compound libraries from tens of thousands to millions of samples. The emphasis was clearly on productivity to keep pace with HTS developments, and not quality. This was not out of choice but out of necessity; the analytical tools required to cope with such an increase in productivity were not available. Consequently, there are major unanswered questions regarding the quality of such libraries. For example, how many samples contain the compound of the correct structure, and at what purity?

As the cost of HTS continues to escalate, many organizations are now considering the option of performing retrospective quality-control checks on their libraries. It is now possible to use high throughput LCMS analysis (~50,000 samples per month) to eliminate poor-quality samples; however, it is not cost effective to perform purification on this scale.

Multi-step solution-phase synthesis – the current trend

The trend is now towards targeted multi-step solution-phase synthesis of tens to hundreds of compounds in support of hit-to-lead programmes. This activity is no longer confined to the 'combichem' group but has been taken up by bench (project) chemists using a range of simple automation tools. It could be argued that this is the most successful achievement to come out of the combichem era.

Reducing project cycle times

There is increasing pressure to reduce project cycle times, and this requires high-quality information to affect decision-making, which, in turn, demands high-quality samples. Chemists want the ability to purify tens to hundreds of compounds in a single batch, obtaining purities >95% with supporting LCMS and NMR data, ideally within the timescale demands of the project.

To achieve this goal, chemists need the right tools, that is, equipment that aids the bench chemist without being a full-time task itself. There is a variety of HPLC purification equipment available on the market; the favoured option being MS-directed purification, which was hailed as the generic solution to all purification problems – crude sample in, press button, pure sample out. Combined with this idyllic view is the desire to run all instrumentation in the synthetic laboratory on a 'walk-up' basis. Personally, I am a great advocate of the walk-up philosophy; in the case of LCMS analysis (for reaction monitoring), it has proved to be successful in giving the bench chemist easy access to high-quality data. The key to the success of 'walk-up' is the small amount of method development or maintenance required. However, the mistake made by some is to believe that this is a short step away from walk-up purification, whereas, in fact, the two are worlds apart.

Embracing new technologies

Interestingly, in the face of all this new technology, many bench chemists have chosen to invest in semi-automated flash chromatography systems. These are much cheaper than LCMS systems but, more importantly, they do not take up much space in the laboratory, are not attached to a computer and can be used to scale up from TLC. Some might argue that this represents resistance to embrace new technology, but chemists will naturally choose equipment that they find to be both productive and easy to use. The flash systems are effective for obtaining milligram to gram quantities of intermediates at a level of 80%–90% purity. However, for purities greater than 95%, reverse-phase

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HPLC is still the preferred technique. The question being considered by many managers now, is whether or not to pursue a walk-up purification strategy or to commit to providing dedicated specialist support.

Before the advent of walk-up LCMS analysis, many research organizations included dedicated MS and chromatography teams. Many of these teams have now been scaled down and, in some cases, disbanded to reflect the change in working practices. Consequently, it is becoming increasingly difficult to provide a service, especially one that has to cope with large fluctuations in workload. Many chemists are now seeing the benefits (time and cost) of having dedicated support to deal with this non-generic problem.

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