Poorly soluble drugs: still a real market opportunity?

Solubilising technologies are at the heart of what drug delivery research is about. An understanding of a formulation is used to improve its performance and add value to an established pharmaceutical compound, or to take a development candidate that has failed because of formulation problems, and make it viable.

There is no doubt that a large and growing demand exists for technologies that improve the solubility of pharmaceutical compounds. In 2000, worldwide sales of poorly soluble drugs were $108 billion, of which compounds with low bioavailability accounted for $57 billion. Last year, 14 of 24 new chemical entities approved were poorly soluble and, currently, 40% of all pipeline compounds are thought to be poorly soluble – although the majority of these are oral formulations with high oral bioavailability.

The number of poorly soluble compounds generated by pharmaceutical companies is expected to increase further as a result of the drug discovery methods they employ, which are increasingly genomics- and proteomics-based, or use high-throughput screening and bio-informatics. The pharma companies have themselves acknowledged the need for cutting-edge delivery technologies for their pipelines. More than one-third of the 75 licensing and acquisition agreements made in 2001 were for the delivery of large molecules or small, poorly soluble molecules.

A recent report from Technology Catalysts International (TCI), *Delivery of Poorly Soluble Drugs*, states: "Poorly soluble drugs, while difficult to work with, represent a unique opportunity for speciality or generic pharmaceutical companies. Potential benefits include improved bioavailability, reduced dosing frequency, reduced pain on injection, and decreased incidence of side-effects. Opportunities exist for product line extensions, including developing a parenteral formulation of a molecule that is currently only available in an oral dosage form."

The report says that there are 132 publicly disclosed products in development that incorporate a poorly soluble drug in a novel drug delivery system. It also identifies 99 poorly soluble drugs with low bioavailability that are candidates for reformulation.

But while it is clear that opportunities exist to improve the solubility of poorly soluble compounds, what are the chances of success in this busy area?

There are more than 70 companies developing solubilising technologies, including Cydex, SkyePharma, Elan and Baxter, which TCI regards as leaders in their field. An example of the type of intense competition that has occurred is with the poorly soluble anticancer compound, paclitaxel. In its conventional form, it must be administered with the solubilising agent, Cremophor, which is responsible for many of the compounds' unpleasant side-effects. However, there are now more than 20 new Cremophor-free paclitaxel products in development.

The success of a company developing a solubilising technology depends on whether it can differentiate itself from the host of competitors. Examining the nature of scientific research in the area, and noting that to improve the solubility of a drug requires a detailed understanding, on the part of the companies, of the specific molecule as well as the technology being used, suggests that there might be enough space for many of them.

It is unlikely that a single technology could be applied to a large number of compounds as a "one size fits all" solution to solubility problems. This is why many distinct approaches have been taken, ranging from chemical conjugation of the molecule to specific functional groups (such as PEG), to complexation – "wrapping" the molecule in another suitable molecule that does dissolve.

In addition to the type of approach taken, the various techniques that are used to achieve the same final result can be a differentiating factor. Nanonisation (reduction of particle size), for example, can be achieved using milling techniques. However, fragile molecules, such as proteins, would be damaged by such a vigorous process. A gentler alternative is supercritical fluid technology. It involves mixing a stream of solution of active compound with the supercritical fluid, which extracts the organic solvent and forms small, dry particles. Furthermore, solubilising poorly soluble drugs often requires "fine tuning or tweaking" of the formulation. Companies with strong, experienced formulation teams would therefore have significant advantages over their competitors, says TCI.

So, this is a crowded market with established and experienced leaders. It could be that any new entrants discover that, unless they have something very special to offer, they have missed the boat. But there is a place for methods to improve solubility that are differentiated not only by the technologies and processes themselves but, since it is a complex and subtle science, by the research teams behind them. The message is that there is huge market potential, but you have to be first-class to get a look in.

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