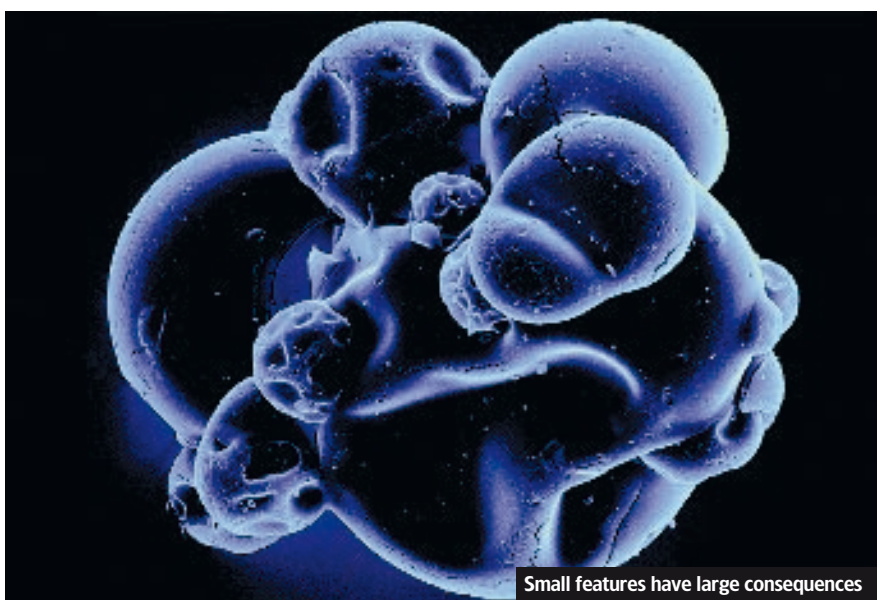
The small stuff

Fine chemical companies add value through the characterization and control of the solid state



Small features have large consequences

CLAY BOSWELL

ALTHOUGH YIELD and purity have always been the first concerns of contractors manufacturing active pharmaceutical ingredients, a small but growing contingent is giving closer attention to issues such as particle size, crystal habit and polymorphism. These and other characteristics of the solid state have typically been left to formulators, but companies such as Hovione, SAFC, Pfanstiehl and Aptuit see an opportunity to add value and differentiate themselves.

SAFC and Aptuit both made solid-state chemistry acquisitions last year. In October, Aptuit purchased SSCI, with facilities in the US and Cambridge, UK. SAFC moved in August, acquiring Cambridge, UK-based Pharmorphix.

"Our focus is to drive molecules into the clinic through understanding and modifying the physical properties of APIs to ensure patient benefit, rapid development and protection of intellectual property," says Chris Frampton, chief scientific officer at SAFC Pharma, Pharmorphix.

"The data that we gather is used to make recommendations as to which solid form our customers should take forward for their drug substance and the reasons why, plus, typically, a recommendation for a second solid form as 'back-up,'" he says.

Solid-form services are useful across the entire life of a drug. "At the primary end, the need for investment is not so critical – at that stage, it's more likely that we would be carrying out what we call 'enabling studies,' which establish sufficient data to take the project to the next level," Frampton says. "It is later in the drug development pipeline that you really need to 'nail down' the solid form."

> **"Later in development you really need to 'nail down' the solid form"**

Post-launch work includes extending the IP surrounding drugs that have come off patent, or "evergreening." For example, if Pharmorphix can find a useful new solid form for an API, a new patent can be issued.

The company also provides litigation support when a patent might be encroached.

ITTY BITTY BY DESIGN

Obtaining the most desirable solid forms – particle design – is not simple, and SAFC may expand the range of tools at its disposal, says David Felker, SAFC vice president. "On a corporate level, SAFC Pharma is actively investigating opportunities to expand its particle engineering technologies through potential acquisitions, along with extending some sizing capabilities at our Madison facility for cytotoxic compounds," he says. Developments are likely in 2008 or so.

Several years ago, Hovione leaped at the opportunity to deepen its own particle design toolkit when Cydex sought to contract cGMP spray drying for its drug-delivery technology, Captisol, used in the formulation of Pfizer's Geodon and Vfend and Bristol-Myers Squibb/Otsuka's Abilify.

Hovione has since acquired one of the most versatile GMP spray-drying units ever built. The company is also developing processes based on supercritical CO_2 and ultrasound.

Guy Villax, CEO of Hovione, sees particle design "at the interface between chemical engineering and phamaceutics," where the product is not a bulk substance, but a collection of tightly controlled, discrete particles.

It is unusual for an API manufacturer to consider the needs of formulators, and visitors from big pharma are often surprised by what they find at Hovione, says Villax. "In their experience [in large pharma], chemists and pharmacists have always worked in silos, and the API is just 'thrown over the fence' in a one-way mode."

Hovione's interest in formulation has extended to the development of an inhaler, FlowCaps, which has been launched in India. Early last month, Hovione announced that Sankyo and Biota had jointly licensed its dry powder inhaler technology for delivery of long-acting neuraminidase inhibitors active against influenza. Hovione has developed a low-cost, disposable inhaler, Twin Caps, specifically for the indication.

"There was significant competition for the Sankyo/Biota project," says Peter Villax, vice president, pharma, "and we were up against very competent inhalation scientists in other specialist laboratories. We got the deal because in terms of offering the entire

range of capabilities necessary for inhaled formulation development, we are the only independent laboratory with experience in all required areas: chemistry, particle technology, powder processing, inhaler technology and deposition testing."

Ferro Pfanstiehl has spent five years developing particle engineering tools that combine the use of supercritical CO_2 with conventional technologies that sometimes cannot handle sophisticated new drugs.

"For example, the milling process has limitations of residual grinding media in the final product," says Pratibhash Chattopadhyay, business director, pharmaceutical technologies at Ferro Pfanstiehl. "The method is also unsuitable for labile material due to the stresses involved during milling. The emulsion antisolvent-precipitation technique as well has the limitation of residual solvents in the final product. These methods are also environmentally cost-intensive due to large waste streams involved during production."

Focusing on the physical properties

Ferro Pfanstiehl's five hybrid technologies are supercritical fluid extraction emulsions; spray freeze-drying with carbon dioxide; supercritical antisolvent with enhanced mixing; particles from gas-saturated solutions; and cryogenic liquid extraction.

The company has cGMP capabilities to provide material suitable for phase I and II clinical trials using most of its technologies, and pilot scale facilities to provide non-GMP-grade material for initial trials.

Ferro Pfanstiehl has performed several successful feasibility projects for pharmaceutical customers. Its objective is to either license the technologies for product development or develop particles as a contractor. "Strategic alliances and joint development of product with pharmaceutical companies are also alternative collaboration opportunities we are seeking," says Chattopadhyay.

BREATHING EASY

"Why do people take tablets?" asks David Hipkiss, CEO of Oxford, UK-based Prosonix.

The API must survive the gastrointestinal (GI) tract, cross the GI/blood barrier, and then the drug's effect might not come for 45 minutes – a long time if, say, one is suffering from a migraine. Injections, though faster, have obvious drawbacks. There is another option, however.

"Historically, formulators have been given [very poor material] to deal with," Hipkiss notes. "If you gave formulators perfectly engineered particles, formulation becomes facile, and it opens up totally new avenues for delivery. You can move away from a tablet, from a parenteral, to systemic delivery through the lungs. For that you need very small, highly engineered crystalline particles which are stable and will fly."

Once reserved for drugs treating the lungs, inhalation delivery is being applied to developmental drugs for cancer, osteoporosis, hay fever and bird flu, to name a few indications.

Effective dosing is not a certainty, however, and the nature of the particles being delivered has a great deal to do with whether they reach the lungs and pass on to the bloodstream or remain in the inhaler. That's where Prosonix comes in.

Hipkiss believes the company's technologies, based on ultrasound-induced crystallization, or what the company calls "sonocrystallization," provide the best means to ideal particles.

"The only way to control crystallization processes is to control nucleation," he explains. "To control nucleation in an even manner, the best way is ultrasound, seeding without seeds, and controlling that at minimal supersaturation where you've got things in control."

Particle size is only one aspect of the problem, he points out. "It's about a combination of size, morphology, surface energy, nanotopology, and critically, particle-particle interaction. To do that, you have to engineer particles to be consistent and the same. That's what we can do, and not many others can, if anybody, at this moment."

Prosonix developed the Prosonitron, a cylindrical ultrasound reactor with circular arrays of ultrasound generators to address the shortcomings of ultrasound probes.

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>
> **David Hipkiss**, CEO, Prosonix

The latest offering is Solution Atomization and sonoXtallization (SAX), developed in cooperation with the University of Bath, in the UK.

In a nutshell, an API is dissolved. The solution is atomized, and as the mist is accelerated down a chamber, most of the solvent is removed, leaving supersaturated droplets 5–10 microns across. As the droplets are dispersed in a nonsolvent, conditions are maintained such that nucleation cannot take place until ultrasonic energy is applied.

"The ultrasonic energy achieves the nucleation of these discrete balls to get exquisite crystalline structures of defined size, surface area, and, critically, the little nanotopologies that push the particles apart and stop them aggregating," says Hipkiss. The nonpolar solvent is stripped away using supercritical CO_2.

"We're left with this beautiful functional white powder, which flows like water," he says. "It has all of the benefits of being nanocrystals, but in a micron size, which you can isolate and formulate."

SAX can also be applied to blends of APIs, with the result that each particle will have exactly the same proportional composition.

"SAX is really in the sweet spot for specialty pharma," he adds. "It's also in the sweet spot for generic players who are being squeezed by the Indian generics and are now trying to reinvent some of their franchises to be specialty companies. And it's in the sweet spot for the major pharmas who want to look at life-cycle extension."

Prosonix has public agreements with Alcoa, Aughinish and, notably, UCB Pharma, which has used the Prosonitron at its GMP pilot plant. "We anticipate moving towards validation, and that the ability for sonocrystallization will be incorporated in a CMC registration dossier," says Hipkiss.

SAX has been short-listed by the Royal Chemical Society for the 2007 Teamwork in Innovation Award, to be announced this month.