Developing Particulate Drug-Delivery Systems

Introducing a Novel Microfluidic Technology

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In response to constant pressure to launch new products onto the market, pharmaceutical and biotechnology companies are spending billions of dollars annually on developing ever more complex and sophisticated therapeutics. However, it is widely acknowledged that many of those therapeutics never reach the clinic. Even the most promising compound can fail clinical trials if unfavorable pharmacokinetics or poor delivery prevents it from reaching its site of action. Controlling the particulate characteristics of a drug formulation is an increasingly important consideration in pharmaceutical manufacturing. It can improve a compound's probability of success by improving availability and reducing dosing. For pharmaceutical companies, an improved formulation offers potential commercial benefits, including increased patient compliance. Companies can extend product lifecycles by using new drug-delivery methods to obtain additional patents on existing products. For companies active in biologics research, precise control over particle characteristics enables development of novel and sophisticated therapies with advanced drug-delivery systems. Examples of particulate-based therapies include Lupron Depot (leuprolide acetate from TAP Pharmaceuticals, www.tap.com) and Nutropin (somatropin from Genentech, www.gene.com).

Product Focus: Particulate delivery systems

Process Focus: Downstream (formulation development)

Who Should Read: Process developers, QA/QC

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Level: Basic

Limitations of Current Technologies

Long-established methods for adjusting bulk powder properties are ubiquitous in the pharmaceutical industry. Spray-formation and lyophilization are considered to be the most reliable technologies for forming particulates. Micronization techniques such as grinding and jet-milling are also commonly used. One fundamental problem with both processes is that they produce broad size-range distributions, in some cases as much as 1–800 µm (**1**). This increases product waste through secondary processing (e.g., sieving and centrifugation), overdosing (to ensure efficacy), and formation of unusable fines. Also, the harsh processing environments required for some techniques can have a detrimental effect on particle integrity, and as a result are incompatible with applications involving delicate substrates (such as live cells). The recent development of supercritical fluid (SCF) processes has produced greatly improved micro- and nanoparticles, with tighter size distributions and in some cases, with valuable resolution of polymorphic products (**2**). However, although spray-formation technologies are quite compatible with large-scale manufacturing applications, SCF (despite impressive recent advances) still struggles to accommodate certain formulations with multi-ton requirements.

Multicircuit microplant under UV
(Q Chip Limited, www.q-chip.com)

A Microfluidic Solution

In response to the current limitations of particle engineering, Q Chip developed a highly controllable and sophisticated process for developing microparticle-based drug-delivery systems using microfluidic chips. Q Chip is the commercial development of innovative research in microfluidic and microplant technologies performed at Cardiff University within the United Kingdom's Department of Trade and Industry (DTI)-led Lab-on-a-Chip (LOC) consortium and a DTI-sponsored Manufacturing Molecule Initiative (MMI). The LOC consortium included leading universities, small- and medium-sized enterprises (SMEs), and large multinationals such as Unilever, GlaxoSmithKline, and Pfizer, with the aim of using miniaturization and acceleration to improve the efficiency of conventional laboratory techniques for analysis and synthesis (**3**). Including

application-focused companies in the consortium provided insight into the requirements for precision-engineered particles in the life science, food, cosmetics, and consumer health industries. Chemical synthesis in µm-sized capillaries allows for precision control over chemical reactions to an extent that would be impossible if performed conventionally in larger vessels. Q Chip's proprietary processing system enables the development of monodisperse microparticles of any size or complexity, offering a step change in particle-engineering technology.

Fluid Flow Properties: The ability to manipulate fluids in such a sophisticated way is predicated upon the unusual properties of fluid flow in microfluidic circuits — in particular, the laminar flow model. At the micron scale, the turbulent fluid flow, which is responsible for fluid mixing, is constrained and, indeed, replaced by laminar flow, whereby fluids move
in planes and with the exception of slow interfacial diffusion, do not undergo mixing. When two immiscible fluids (under pressure) are brought into contact in a microfluidic circuit, *segmented flow* results, producing alternate, discreet quanta of the two component fluids (Photo 1) (**4**). Q Chip uses the extraordinary properties of immiscible fluids flowing in microchannels to precisely control fluids in accurately constructed circuits.

However, this novel approach to fluid handling departs from materials historically used in microfluidics such as glass, steel, and silicon and instead uses hydrophobic polymer waferchips as a platform for fluidics research. The advantages of using these particular polymer surfaces are several. They are completely bioinert and antifouling, making them ideally suited to biopharmaceutical processing and manufacturing. The waferchips themselves are relatively inexpensive and completely disposable. What is most important, the polymers enable establishment of segmented flow conditions with an unsurpassed level of stability and reliability, which can thereby be used to elute nano- or even picoliter volumes of fluids uniformly and reproducibly. By combining any number of modular "plug-and-play" fluidic architectures, Q Chip designs and fabricates client-specific microplants. These devices enable thousands of nano-scale chemical reactions to take place simultaneously with unparalleled precision. Q Chip uses this principle to produce monodisperse microparticles (Photos 2 and 3).

The technology offers more than just a sophisticated processing environment. Precision microparticle production relies on the accurate control of nano- to picoliter fluid volumes; hence, any chemical reaction that occurs in the liquid, solution, or molten phase can potentially be translated to the microreactor platform. With multiple fluid input points, even complex chemical reactions are possible. The microreactor itself is constructed from a material with high chemical resistivity, which allows manipulation of even aggressive reagents such as strong acids and bases. That enables the development of novel chemistries, offering clients new delivery and dosing possibilities.

To produce microparticles, a phase change (liquid → solid) must take place. Because a Q Chip microreactor is custom designed for each specific chemical reaction, the reaction and residence times required for this phase change are carefully accounted for. This permits synthesis of a range of microparticle types through polymerization and cross-linking (either thermally or photochemically initiated), by precipitation (upon addition of an antisolvent or introduction of an insoluble chemical moiety), or simply by heating and cooling to melt and reform a low-melting-point solid material. Also, the nanoliter fluid quanta may themselves be accurately dispensed solutions of a pharmaceutical or active ingredient, which can be subsequently encapsulated with a protective membrane or coating. Possible coatings include food-safe formulations of biodegradable polymers such as polylactide and glutamate, polysaccharides (e.g., pectin, alginate, and dextran), or polyamino acids. Q Chip can also produce complex multicoated particles by manipulating several of these substances in sequence to impart valuable sustained-release characteristics to products. Again using biocompatible polymers, Q Chip creates monodisperse cross-linked hydrogel microspheres, which can be loaded with sensitive biologics such as proteins, DNA, and even live cells.

Microparticle size control is important in a growing number of drugs, in particular deep-pulmonary inhalation therapies. This type of treatment is already available, but not without serious problems relating to variation in particle size. Larger particles deposit in the respiratory tract before reaching the deep lung, and smaller particles aggregate or become phagocytosed. Consequently, it is necessary to overdose significantly to ensure efficacy of a particular therapeutic — a wasteful and costly process. Q Chip's ongoing research program is focused on size reduction programs to enable development and manufacture of <5-µm particles within a narrow size distribution to reduce costs and increase efficacy.

As with other microparticle engineering technologies, however flexible the methodology may be, it must still aim to contend with existing large-scale manufacturing processes. How can a fundamentally small-scale technology hope to satisfy global volume requirements? Q Chip handles the issues of scale-up and industrial-scale manufacture in unique way. Using its microfluidic platform, Q Chip creates monodisperse microparticles in precision engineered, microfluidic circuits. Working alone, a single fluidic circuit may produce only small volumes of particles (for analysis or feasibility studies). Yet with intelligent fluid distribution and handling, they can be integrated in parallel to produce massively parallel arrays of circuits. So although a "conventional" large-scale, continuously fed reactor can produce several tons of polydisperse particles, Q Chip proposes the microplant: a considerably less spatially demanding device designed to house and feed an intricate system of stacked wafers, into which circuit arrays are micro-machined (Photo 4). With thousands or potentially millions of facsimile circuits working in unison, ton quantities of microparticles are readily attainable, with (crucially) an overall product size distribution of less than 1%.

Q Chip approaches microparticle production in a new way. The company does not manufacture particles per se but develops custom microfluidic systems and microplants for installation at a client site (or preferred third-party manufacturing partner) under license. An understanding of the client's requirements and synthetic strategy allows Q Chip to create a microfluidic solution by converging expertise in

Photo 1: Segmented flow

Photo 2: Microparticle production environment

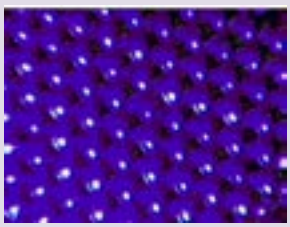

Photo 3: Monodisperse polymer hydrogel microparticles (400 µm ± 1%)

Photo 4: Single and multicircuit microplants

chemistry, biology, and microtechnology. Using Q Chip's knowledge of precision engineering and microfabrication, a feasibility-scale microreactor is manufactured, then scaled out with established fluid-distribution systems. Hence, a room-sized continuously stirred reactor is replaced by a bench-top microplant, custom designed to produce high-value, monodisperse particles of exactly the correct size, shape, and three-dimensional structure.

Improving Efficacy

The trend toward increasing use of monodisperse microparticles for higher quality products with improved efficacy will continue to drive the need for improved particle processing systems. With this in mind, Q Chip's microfluidics platform is well placed to offer a step change improvement in the development and manufacture of particulate-based drug-delivery systems.

References

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