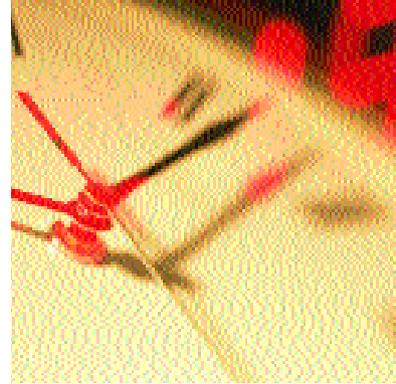


Rita D'Aquino

# Masterminding Mixing Technology



Mixing isn't exactly the most titillating topic, but it is an essential operation in the chemical process industries. Not only that, but it also has a substantial impact on a manufacturer's bottom line. In 1993, a major U.S.-based chemical company estimated that the value of mixing to the firm was in excess of \$25 million annually. A recently published handbook on industrial mixing (see p. 47 for a review of the book) estimates the cost of poor mixing to be as high as \$100 million/yr.

Mixing equipment has matured over the years and is now in an evolutionary state. New developments in design and performance are being driven by the characteristics of the product being manufactured. Today, formulations are becoming increasingly complex and viscous, and where a product's fluid characteristics are essential to its functionality (e.g., sunscreen, liquid detergents and conditioners), the rheology can be highly intricate. "In these cases, it is often essential to apply much higher shear rates than those achievable in agitated vessels, which drives the industries towards rotor-stator and similar devices," says Michael Butcher, marketing director of BHR Group's Fluid Engineering Centre (Bedfordshire, U.K.; [www.bhrgroup.com](http://www.bhrgroup.com)).

The distinguishing feature of a rotor-stator (R-S) mixer is a high-speed rotor in close proximity to a stator (Figure 1). Typical rotor tip speeds range from 10–50 m/s. They are also called high-shear devices because the local shear rate they can achieve in a vessel (20,000–100,000 1/s) is much greater than that which is possible by a mechanical agitator. Charles Ross & Son Co. (Hauppauge, NY; [www.mixers.com](http://www.mixers.com)) offers an ultra-high-shear in-line R-S device called the MegaShear that can do everything from dispersion to disintegration of difficult solids, such



Figure 1. A typical rotor-stator mixing device.

as polymers and elastomers, converting them into submicron-sized particles in a single pass. As fluid enters the center of the stator, pumping vanes on the rotor, which spin at 55 m/s, accelerate the product through grooves in the respective parts, but in opposite directions, "the result being an opposed flow collision that imparts tremendous shear forces upon the product," says Doug Cohen, vice president of technical services at Ross.

A secondary trend is the goal of using a high-shear mixer to disperse a dry powder directly into the flow of a liquid, replacing older design concepts that relied on an additional pump to transport solids from the solids educator to the mixer. "This is a critical issue because many powders are extremely hard to disperse efficiently, and conventional technology was prone to persistent clogging and slow induction rates, which always drove up cost while they drove down throughput," says Scott Anderson, IKAWorks' (Wilmington, NC; [www.ikausa.com](http://www.ikausa.com)) technical services manager. The firm's multipurpose homogenizer and disperser, the MHD 2000 utilizes an auger and paddle in place of a venturi device to feed the solids into the mixing chamber at rates

of up to 700 lb/min, while wetting out resins, polymers and other materials that have viscosities of up to several hundred thousand cP — a feature that is not feasible with vacuum-type systems. It also significantly reduces aeration of the product.

"Rotor-stator mixer technology has been refined as opposed to revolutionized over the last 10 years," says Arthur Etchells, III, a mixing consultant with DuPont Corp. (Wilmington, DE; [www.dupont.com](http://www.dupont.com)). "What has changed drastically is our understanding of its design and operation, mostly through a trial-and-error approach to process development and scaleup, because there is no fundamental basis for this mixer's performance," he continues. Bridging the gap are two consortia, BHR's Fluid Mixing Processes Research Consortium and the high-shear mixing research program spearheaded by Richard Calabrese at the Univ. of Maryland (College Park, MD; [www.umd.edu](http://www.umd.edu)). Both have engaged in research and development to elucidate the complex hydrodynamic environment in R-S devices.

### Gaining a deeper understanding

Computational fluid dynamics (CFD) has become an essential tool, along with conventional and new experimental techniques, in the conceptualization, scaleup and understanding of mixer performance. "However, time-dependent mixing flows, coupled with complex geometry, bring uncertainty to the CFD predictions, especially for turbulent flows," says Calabrese. "Models that couple the local reaction and mixing processes allow the simulation of the spatial variations of concentrations due to mixing and diffusion and thus, the rates of chemical reaction."

CFD software companies have put more options into their packages to help users build a more realistic mod-

el of the flow field in the vessel. This includes the use of using velocity input from the outlet of the impeller obtained by techniques such as laser Doppler velocimetry (LDV). Particle image velocimetry (PIV) has evolved to be a powerful technique for 2D and 3D whole-field velocity measurements and is especially useful for examining instantaneous spatial shear rates, but it is not as accurate as LDV for time-averaged measurements.

CFD is touted as a helpful tool in vendors' efforts, as well. Once an agitator is designed at Chemineer, Inc. (Dayton, OH; [www.chemineer.com](http://www.chemineer.com)), the file may be sent to a preprocessor that sets up all the required information for the CFD software, including the grid and boundary conditions. The output is standardized and sent to the agitator designer. "It has proven most beneficial when designing agitators for non-Newtonian fluids," says Julian Fasano, director of engineering and development at Chemineer. David Dickey, senior consultant at MixTech, Inc. (Dayton, OH; [www.mixtech.com](http://www.mixtech.com)), isn't as quick to praise the benefits of CFD. "With regard to high-shear applications, CFD has only been shown as a research tool for tracking flows in R-S mixers. Regardless of the sales pitches, it does not work well in multiphase, dispersed, or non-Newtonian fluids."

One challenge with CFD is often the lack of data to validate the results. "In such situations, analysts must count on engineering knowledge and experience," adds Victor Atiemo-Obeng, scientist, engineering and market development, Dow Chemical.

### Designing around scaleup issues

Scaleup methods for batch and semibatch mixing systems have been modeled extensively. However characterization of the physical and chemical parameters of multiphase systems with complex reactants and interfacial phenomena is extremely difficult and may limit the usefulness of these correlations, especially for CFD simulation. "One of the most difficult aspects of scaleup in homogeneous and heterogeneous reactions is the prediction and

control of byproduct distribution.

"These byproducts may be negligible on the lab or pilot scale, but may increase upon scaleup to production. An increase of as little as 0.1–1% in the amount of a particular byproduct may not be acceptable when it cannot be adequately removed

by downstream processing," says Etchells. These impurities may affect the physical form, particle size, downstream liquid–liquid separation or foaming tendency of the product.

"The problem is that when scaling up, people do not always recognize the critical factors involved in the basic process — *e.g.*, proper heat and mass transfer, especially if fast reactions are occurring," Etchells continues.

In conventional emulsions processing, critical parameters, such as mixing energy, mixing time, and heating or cooling times, are not easily transferred from the laboratory to production. With Velocys, Inc.'s (Plain City, OH; [www.velocys.com](http://www.velocys.com)) microchannel emulsifier, which creates dispersions for the coatings, food, and cosmetics industries, these parameters remain constant for all scales of processing.

During operation, the discontinuous and continuous phases enter the device and flow in alternating microchannels measuring 250–5,000- $\mu\text{m}$  in dia. (Figure 2). The discontinuous phase flows through a porous substrate and forms droplets less than 1,000 nm that are clipped by the continuous phase, creating the emulsion, which exits through one outlet port. The system operates at temperatures in the range of 80–200°C, and at low pressures. "An emulsion might be made at 50 psig, compared to 2,000 psig in a homogenizer," says Laura Silva, manager of business development at Velocys. Pressure drops are 1–10 bar,

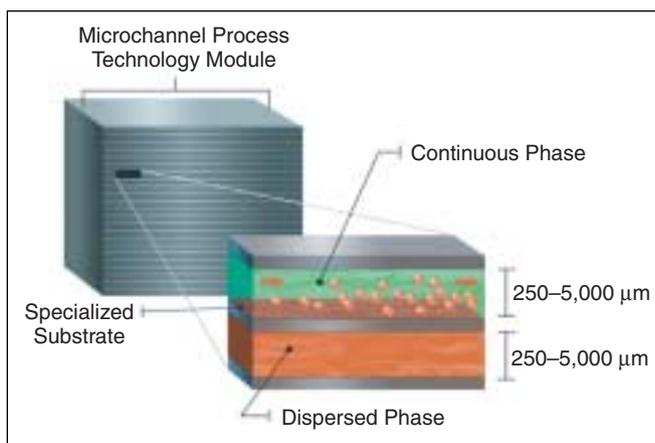


Figure 2. Velocys' continuous multiple stream mixer reactor achieves macro-meso- and micro-mixing, while tightly controlling particle size and purity.

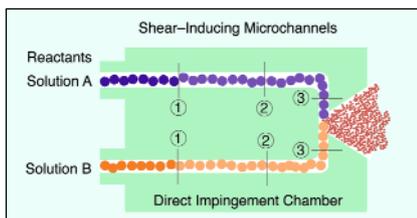
with services up to 10,000 L/h.

A similar system was unveiled in 2003 by the Institut für Mikrotechnik Mainz GmbH (Germany; [www.imm-mainz.de](http://www.imm-mainz.de)). Called the StarLaminator, it is a micromixer capable of handling flowrates of up to 300 L/h at a pressure loss of 12 bar. The complete unit, with dimensions of 45 × 25 × 30 mm<sup>3</sup>, consists of a stack of 320–1,600 mixing foils measuring 50  $\mu\text{m}$  thick. The foils have microchannels with three different patterns. With a careful choice of the sequence, both educts are fed alternately in thin layers to a central channel, where the streams merge to become thin fluid sheaths. Mixing occurs via diffusion through the sheaths, then by secondary turbulence, depending on process conditions.

### Moving towards continuity

Where process conditions and scale of operation allow, there is a move towards inline continuous mixing and even chemical reactions, which would allow the ability to control the reacting environment much more closely, thus permitting higher mixing and heat removal rates, elevated operating pressures, and more successful scaleup. "It is a form of process intensification that often allows reaction routes not possible within the constraints of stirred tanks, and it also requires less space," says BHR's Butcher.

"In the fine chemical industry, most reaction chemistry is done in batch reactors, where scaleup usually requires multiple units and presents risks of



**Figure 3.** Microfluidics' multiple liquid mixer/reactor (MMR) is designed to achieve (1) macro-mixing, (2) meso-mixing and (3) micro-mixing. For very fast reactions, intense micromixing is achieved in a matter of microseconds.

batch inconsistency," says Irv Gruverman, CEO of Microfluidics, Inc. (Newton, MA; [www.microfluidicscorp.com](http://www.microfluidicscorp.com)). The firm recently commercialized a multiple stream mixer/reactor (MMR), based on its microfluidizer platform, that continuously produces uniform nanoparticles using multiple reactant fluid streams in an ultraturbulent reaction zone. "The MMR optimizes fast chemical reactions and can be scaled easily to commercial production without losing product quality, since the equipment geometry does not change," Gruverman continues.

Current applications include making nanosuspensions for intravenous delivery of pharmaceutical insoluble actives, high-purity metal oxides for the electronics industry and drugs nanoencapsulated in polymers, according to Mimi Panagiotou, Microfluidics' director of R&D. "We built a prototype comprising two microfluidizers operating in parallel that delivers <1 L/min of product and expect to scale this system to 8–10 L/min without difficulty," she says.

Multiple reactant streams are fed in stoichiometric ratios at up to 40,000 psi through a pencil-eraser-sized channel within the mixing chamber. Flow is directed into nanometer-length inlet channels (0.01–0.05 cm<sup>2</sup>), where fluid velocities of 3–30 m/sec are reached and maintained for tens of milliseconds, creating a small amount of microcrystalline product nuclei to seed the reaction. The streams enter a second set of narrower channels (0.0001–0.001 cm<sup>2</sup>) at 80–300 m/sec and mix for a few milliseconds before being released to a relatively large exit channel.

Depending on optimum conditions for a reaction, the geometry features

macro-, meso-, and micromixing regimes (Figure 3). In the case of a very fast reaction, the degree of micromixing is maximized, generating energy dissipation values on the order of 10<sup>8</sup>–10<sup>10</sup> W/kg, "far greater than that achieved near the impeller in any stirred tank reactor, homogenizer or R-S mixers," says Gruverman. The products are nanoparticles in the 10–100 nm size range, and can usually be held within ±10% of the target particle size.

### Shifting expertise

Many vendors and users acknowledge a downward trend in new products and services, in part due to mergers and acquisitions, such as the recent unification of Bran+Luebbe, Lightnin and Waukesha Cherry-Burrell to create SPX Process Equipment, Inc. (Delavan, WI [www.spxprocessequipment.com](http://www.spxprocessequipment.com)), and

Sulzer Chemtech's (Winterthur, Switzerland; [www.sulzerchemtech.com](http://www.sulzerchemtech.com)) purchase of the mixer business of Koch-Glitsch. Users have cut their own engineering staffs, and now rely more on vendors or consultants to handle processing issues that in the past would have been handled in-house. "Ten years ago, we had ten in-house mixing experts. Today we have two," says I-Hwa Midey Chang-Mateu, director of coatings process technology at Rohm & Haas Co. (Philadelphia, PA; [www.rohmhaas.com](http://www.rohmhaas.com)). "Much of the capital budget has been allocated to addressing security concerns," she adds.

Furthermore, with the large decline in sales for mixers in the past few years, vendors have reduced, or even eliminated, research in mixer technology. Consequently, says Shaffiq Jaffer, senior engineer and mixing

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specialist for Procter and Gamble's (P&G; West Chester, OH; [www.pg.com](http://www.pg.com)) corporate engineering technical laboratories, some users are becoming more of the expert on the mixing equipment than the vendors from whom it was purchased. "A large part of being successful in developing new processes for existing hardware is leveraging external capability — linking up with consortia and academia," he says. "When it comes to allocating resources, mixing equipment R&D is not a priority. At P&G, it accounts for much less than 1% of the R&D budget (which is 3–5% of the outside sales)."

Against this backdrop, mixing equipment design has gone beyond mechanical and costing considerations, with the primary objective being how best to achieve the key mixing process objectives, says Edward Paul, a mixing expert who recently retired from Merck & Co. (Rahway, NJ; [www.merck.com](http://www.merck.com)).

## Growing markets

In the pharmaceutical industry, impinging jets mixer/crystallizer technology has come of age. Merck holds the original patent for crystallization of pharmaceuticals using an impinging-jets mixer, where reactants in a solvent precipitate are mixed with an anti-solvent (or non-solvent) via the collision of opposed jet streams to achieve a particle size of ~5–20  $\mu\text{m}$ . "Intense micromixing and high supersaturation is responsible for the rapid crystallization of monodisperse micron sized particles, which exhibit improved bioavailability and stability," says Merck's Brian Johnson, who is responsible for the scaleup of processes that make pharmaceutical ingredients. Merck, which also patented the production equipment, is currently using the technology for the production of a commercial drug product.

In 2003, Pfizer patented the use of impinging jets for a reactive crystallization where two streams react in a rapid mixer and then crystallize to produce the pharmaceutical. To avoid infringement on Merck's intellectual property in future inventions, Pfizer

has applied for a patent on an impinging plate device.

Meanwhile, Bristol Myers Squibb Co. (Princeton, NJ; [www.bms.com](http://www.bms.com)) recently patented a technology for creating submicron crystals of a drug that involves two impinging liquid jets are positioned within a flask that is sonicated near the jet-impingement point by a 20-kHz probe. The ultrasound is claimed to enhance the mixing process and promote the formation of crystals smaller than that which is possible with the impinging jets alone.

Over the last five years, Robert Prudhomme, a Univ. of Princeton researcher, and Johnson have developed a process they call Flash Nanoprecipitation, where rapid mixing of reactant streams containing colloidal stabilizers is performed in an analytical, confined impinging jets (CIJ) mixer to produce nanoparticles of pharmaceutical agents. The system, which has been qualified, requires a mixing time well below 100 ms for ideal nanoparticle formation. "We have quantitatively shown that the time for mixing should be less than the time for precipitation, for optimum performance — hence, the need for specialty designed high intensity mixers to produce uniform and small particles," says Johnson.

In the plastics industry, manufacturers have sought to improve the properties of commodity plastics by mixing them with another plastic or additive. "A shortcoming of existing mixing technology is that only a limited variety of blend morphologies are producible at low compositions of a property modifier," says Dave Zumbrunnen, professor of mechanical engineering at Clemson Univ. (SC; [www.clemson.edu](http://www.clemson.edu)). To overcome this, Zumbrunnen and a team of researchers at Clemson developed a continuous blending device called the SmartBlender, which produces polymer blends with novel properties by folding the two melts together, rather than by distributing one evenly throughout the other.

The device uses a principle of fluid dynamics known as chaotic advection

to repeatedly fold a masterbatch or other component into a matrix polymer, forming a variety of controlled and repeatable polymer morphologies, from layers, ribbons and platelets to spongy interpenetrating structures. In a typical run, material is fed by two 0.75-in.-dia. single-screw extruders into a crosshead die from opposite ends and into a distribution head. The matrix material passes through a single central port, while the secondary resin or masterbatch goes through nine small ports arranged in a circle around the central one.

From the distribution head, the material enters a cylindrical blending chamber containing two 22-mm-dia. stirring rods that are programmed for a sequence of speed and/or directional changes — *i.e.*, they take turns spinning three times faster than the other for a specific number of turns. Changing the rod rotation protocol can produce blends of differing morphologies without any type of equipment modification.

Clemson researchers have used the technology "to produce sponge-like blends of immiscible polymers, such as polypropylene (PP) and low-density polyethylene (LDPE) over broader compositional ranges (*e.g.*, 70%:30% by vol.) than are achievable with conventional compounding equipment, yielding morphologies that improve PP's normally poor cold impact strength," he says. In this case, chaotic advection stretches and folds thinner and thinner layers of LDPE in the PP matrix. After repeated layering, the LDPE layers become so thin, they eventually rupture, letting the PP flow through the holes in the LDPE. Holes also form in the PP layers, creating a fibrous spongy structure out of the stiffer PP.

Zumbrunnen says that the team is now performing developmental work with plastics for specific clients, extruding these materials into films and sheets for companies to test in their own labs. At least one machine supplier has been selected to produce commercial-scale equipment, and more agreements are expected in the near future.



## PROCESS TECHNOLOGY

### Participants Needed for Feasibility Study on Vinyl Recovery Process

A study by Teknor Apex (Pawtucket, RI; [www.teknorapex.com](http://www.teknorapex.com)) to be completed by 2004 could lead to construction of a U.S. plant that uses Solvay S.A.'s ([www.solvay-plastics.com](http://www.solvay-plastics.com)) Vinyloop technology for recovering and recycling flexible vinyl compound from wire, cable, coated fabric, and other composites that until now have proven difficult to recover economically from the constituent materials.

During the Vinyloop process, polyvinyl chloride (PVC) waste is first reduced in size, granulated and dissolved in proprietary solvents. This separates the vinyl from other materials and precipitates microgranules containing PVC resin and additives, such as plasticizers and stabilizers. The solvents are completely regenerated.

Teknor Apex is seeking input from potential participants who could supply annual resource streams in excess of 250,000 lb/yr of the vinyl component and would buy back the recovered vinyl at 70–80% of the original cost. Besides wire-and-cable companies, Participants may include manufacturers of automotive instrument panel skins, wall coverings and flooring, says Peter Galland, Vinyloop project manager for Teknor Apex.

Solvay started a \$13 million demonstration facility based on the process in 2002 in Ferrara, Italy. This plant has a nominal capacity to recover 19 million lb/yr of vinyl compound from 22 million lb/yr of waste. The recycled material can be sold at prices close to those of new raw materials.

Recently, Solvay and a venture partner in Japan announced plans to build a commercial-scale Vinyloop plant in Japan, with startup planned for 2005. Solvay is working on a second generation technology of Vinyloop that should reduce investment by 20% and energy consumption by 25%.

### High-Solids Coating Keeps Wood at Its Prime

Akzo Nobel N.V. (Arnhem, Netherlands; [www.deco.akzonobel.com](http://www.deco.akzonobel.com)), through its Decorative Coatings Europe (DCE) business unit, has developed a water-based wood coating called Nordsjö Tinova VX that has nearly twice the amount of solids by volume — or 65% — than competing waterborne decorative coatings.

The coating employs an alkyd/acrylic resin system that is formulated using a waterborne high-solids (WBHS) technology (U.S. Patent No. 6,277,910 B1 and EP No. 0874875 B1) in which the water of a standard polymer dispersion serves as the emulsification media for a second resin.

“The high-solids content obviates the need for coalescing solvents typically needed for film formation, and reduces Tinova VX’s volatile organic compound (VOC) concentration to less than 20 g/L,” explains Jørgen Olsen, Nordic R&D manager for Akzo Nobel DCE. This makes the product compliant with European Union regulations that will limit VOCs in decorative coatings to 150 g/L by 2007 and to 130 g/L by 2010.

“In addition, only two coats are required for complete coverage vs. three with conventional products,” says Kees den Elzen, international marketing manager for Akzo Nobel DCE. “Since 80% of a paint job’s costs are due to labor, a 33% reduction of this cost is economically attractive, even though Tinova VX is likely to cost more than competing products.” Tinova VX is available in the Nordic countries and will launch in several European markets and in North America by 2005–2006.

### Complete Oil Extraction

More than 60% of all known oil reserves in the U.S. remain untapped because of the high cost of extracting oil from marginal wells — those in which production has slowed to 15 bbl/d or less. Now, Sequoia Interests Corp. (Richmond, TX; [www.sqproducts.com](http://www.sqproducts.com)) has developed an inorganic silicon polymer called DiamondFlo that recovers more than 80% of oil from a depleted oil-bearing formation. Pumped as a 2–5% active aqueous solution into the substrate, it adsorbs on solid surfaces, displacing oil, rather than emulsifying it into water, so it can be recovered separately.

DiamondFlo is currently produced in 10-L reactors dur-

## Engineering Solutions

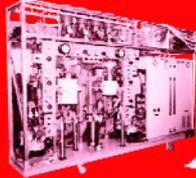
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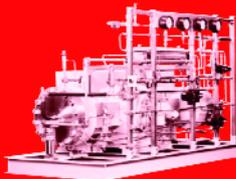
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## SOFTWARE &amp; INSTRUMENTATION

## Software Minimizes Impact of Market Variability on Supply Chain

SherTrack LLC (Livonia, MI; [www.shertrack.com](http://www.shertrack.com)), a two-year-old software enterprise, has launched its first commercial product — an inventory planning and production scheduling solution called SNAPPS. The software uses statistical process control (SPC) techniques and probabilistic analyses to sense subtle changes in market conditions and adapt to the day-to-day variability and uncertainty in manufacturing operations. An acronym for “sense and adapt probabilistic planning and scheduling,” SNAPPS is designed to dovetail with leading enterprise resource planning (ERP) and advanced planning and optimization (APO) solutions, such as those offered by SAP AG (Walldorf, Germany; [www.sap.com](http://www.sap.com)), to produce optimized schedules over a 0–6-wk time frame.

Traditional optimization techniques for supply and demand are designed to meet the “single number” forecast of how much of each product should be produced and sold in the coming days, weeks and months, requiring a manual response to market fluctuations.

Emulating human judgment, SNAPPS’s probabilistic scheduling and planning model uses a company’s ERP

data in conjunction with market demands, inventory planning, supplier variability, and detailed production and scheduling information to characterize the “behavior” of a production operation. When a change occurs, the probabilistic models are automatically updated to track subtle changes in market conditions, allocate limited production capacity, meet service targets and reduce inventory.

In addition, SNAPPS software includes a scenario-planning environment that allows one to simulate critical supply-chain events, like new product introductions, sales promotions and plant shutdowns, to track business metrics and compare the performance of different planning options.

“Customers that deploy SNAPPS typically achieve tangible results within a fiscal quarter,” says SherTrack’s vice president of professional services, Colin Wearing. Based on pilot testing with chemical companies, SNAPPS delivers a return-on-investment (ROI) in 8–12 wk in the form of improved customer service, increased asset and employee productivity and fewer production changeovers,” he notes. One chemical plant boosted its percentage of orders shipped on time from 98% to 99%, while reducing inventory by 33%. SNAPPS’s pricing ranges from \$50,000–\$250,000 per production line, and is scaled according to its real ROI, notes Wearing.

ing a sequential endothermic/ exothermic batch reaction that takes place at 1 atm and an initial temperature of 27°C. Silicon granules are loaded into the reactor, and just enough water is added to cover them. A blend of proprietary chemicals (including one that prevents runaway reactions) is added at a specific ratio to silicon, initiating an endothermic reaction during which monomers are formed.

The temperature rapidly increases to 110°C as the monomers auto-catalytically polymerize into a viscous liquid with a specific gravity of 1.5, a pH of 12–13 and the consistency of corn syrup. The reaction is completed in 6–12 h and consumes approximately 25% of the original silicon. As this liquid is drawn off the bottom of the reactor, silicon is recharged to the reactor and the process is repeated.

The polymer’s structure is being analyzed using nuclear magnetic resonance (NMR) imaging at the Univ. of Houston (TX; [www.uh.edu](http://www.uh.edu)) under the direction of chemistry professor Charles Anderson. “The polymer appears to comprise a silicon backbone with attached surface active agents and is estimated to have a molecular weight of 50,000–100,000. In addition,

it appears to be biologically inert, stable to over 100°C and innocuous at the current dosage concentration,” he says.

An independent R&D organization in San Antonio, TX, is evaluating the product for other applications, such as the displacement of hydrocarbons from equipment — *i.e.*, bottoms of distillation columns — and to remediate soils by displacing organics (*e.g.*, PCBs, toluene and benzene).

EFIRD Corrosion International, Inc. (ECI; The Woodlands, TX; [www.efirdcor.com](http://www.efirdcor.com)) is working with Sequoia to increase production from the laboratory to the 1,000-gal scale by the end of Sept. in preparation for field trials. “The first commercial products will be released at that time at a cost of \$10–12/gal, which is competitive with other current fluids designed to increase production,” speculates Kurt Neubauer, business development consultant for Sequoia. Research is also underway at EFIRD to determine the polymer’s dehydration and reconstitution characteristics. “If DiamondFlo retains its properties upon re-hydration, Sequoia will be able to ship it as flakes that can be reconstituted onsite,” says Daniel Efird, president of ECI.

## R&amp;D UPDATE

## Optimizing Protein Crystallization for Low-Volume Solutions

Univ. of Chicago (IL; [www.uchicago.edu](http://www.uchicago.edu)) researchers led by Rustem Ismagilov have demonstrated a new composite microfluidic system for crystallizing proteins within nanoliter to picoliter-size aqueous droplets, thereby eliminating manual handling of the crystals (*Angewandte Chemie*, **43** (19)). “The spatial structure of a protein is critical to the way it interacts with small molecules, which is a key concern of pharmaceutical researchers, says Ismagilov. The structure is usually

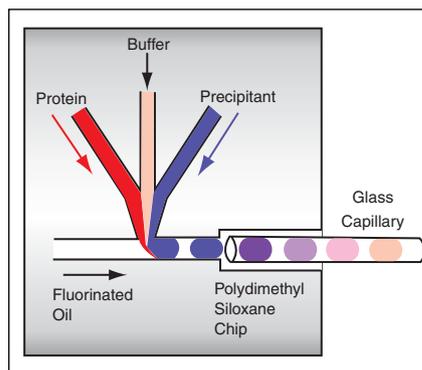


Figure 1. Droplets with varying protein concentrations, depicted by different shades of red, are formed via the composite microfluidic device.



determined by x-ray diffraction, which requires a high-quality crystal. But crystallization of many proteins is difficult.

Ismagilov's technique is based on a thumbnail-sized chip constructed of polydimethyl siloxane (PDMS). The chip features 200- $\mu\text{m}$ -dia channels that facilitate the formation and transportation of aqueous droplets, and a 200  $\times$  200- $\mu\text{m}$ -dia glass capillary into which the droplets are injected after formation. The scientists are now using the system to crystallize novel, uncharacterized proteins and protein/ligand complexes that have not shown good results with traditional crystallization methods.

Syringe pumps flow aqueous solutions of a protein, a precipitation agent, and a buffer solution through separate channels (Figure 1) which merge to form nanoliter droplets in a center channel filled with a water-permeable, fluorinated siloxane polymer oil. The droplets are carried by the oil into a glass capillary that is attached to the edge of the PDMS chip. Crystals are formed either upon simple incubation of the solution, or as a result of the removal of water from the protein droplets by vapor-diffusion.

To enable vapor diffusion, Ismagilov sets up a second system of side-channels that generates an alternating sequence of droplets in the oil-filled capillary tube. The first droplet contains lysozyme and precipitants and the second set contains a high concentration of salt. Water molecules diffuse out of the protein-containing drops, then through the oil, and finally to the drops with the higher salt concentration. The protein-containing drops shrink, increasing their protein concentration and causing nucleation of the protein crystal. Crystals then grow from the nuclei.

When the glass capillary is filled with alternating drops, it is disconnected from the chip, sealed with wax, incubated at 18°C, and monitored. "After 2 days, more than half of the 10–20-nL droplets yielded crystals measuring 50–200 nm on each side — large enough for synchrotron diffraction experiments," says Ismagilov.

Aqueous evaporation through PDMS is a known problem, but Ismagilov notes that even without humidity control during incubation, his droplets showed no signs of evaporation from the capillary for up to 6 months.

## BIOTECHNOLOGY

### FDA-Approved Test for Anthrax Detection Now Available

In June, Immunetics, Inc. (Boston, MA; [www.immunetics.com](http://www.immunetics.com)), received approval from the Food and Drug Administration (FDA; Rockville, MD; [www.fda.gov](http://www.fda.gov)) for a new test that assesses whether individuals have been infected with anthrax, a disease caused by *Bacillus anthracis*. This enzyme-linked immunosorbent assay (ELISA) called QuickELISA Anthrax-PA is the first test to be approved by the FDA for direct use on patient blood specimens for anthrax detection. "It improves upon testing methods developed by the Centers for Disease Control and Prevention (CDC; Atlanta, GA; [www.cdc.gov](http://www.cdc.gov)) by requiring 45 min for completion vs. about 4 h," says Andrew Levin, Immunetics' chief executive officer.

QuickELISA confirms a diagnosis of anthrax by detecting antibodies produced by a person's immune system to the protective antigen (PA), a protein produced by *B. anthracis*. During testing, a 10- $\mu\text{L}$  sample of blood serum is transferred to a plastic microplate containing an 8  $\times$  12 array of wells that are pretreated with assay-specific reagents. In the presence of anthrax antibodies (AAs), the microplate wells bind an enzyme which produces a colored product. After 25 min of incubation followed by rinsing, an enzyme substrate is added. The solution turns blue if AAs are detected and remains clear if they are not. Addition of a stop reagent changes the reaction product from blue to yellow and the final absorbance is read by an ELISA reader (a spectrophotometer adapted to read 96-well microplates).

Concurrently, positive and negative controls are run in duplicate on the same microplate. An assay cut-off is generated by adding 0.1 to the negative control average absorbance. Any sample with an absorbance greater than the cutoff number has tested positive for anthrax. "The test was shown to detect 100% of the anthrax patients tested in clinical trials, with less than a 1% chance of false positive results," says Levin.

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## REGULATORY UPDATE

### Toxic Releases Continue on a Downward Trend

The U.S. EPA (Washington, DC; [www.epa.gov](http://www.epa.gov)) recently issued the 2002 Toxic Release Inventory (TRI) — the annual report on the amount of toxic chemicals released into the environment. The report shows that toxic chemical releases continue to decline across the U.S. Total releases to the air, water, and land in 2001 were 4.79 billion lb nationwide, which is 15%, or 819 million lb, lower than the amount reported in 2001. Based on the trends since the inception of TRI in 1988, chemical releases have decreased approximately 49% (Figure). This year, the TRI is reported in a new format that does not collect any new or different information, but rather clearly identifies the categories for reporting releases and other waste-management activities of toxic chemicals.

Of the 4.79 billion lb of releases reported, 89% were released onsite and 11% were released offsite. Of the onsite releases, about 34% of the chemicals were released to air, 5% to water, 5% to underground-injection wells, and 56% to land-disposal facilities.

As in previous years, releases from the metal mining industry in 2001 made up a substantial portion of all chemical releases — 27%. However, this industry also had the largest absolute drop — 971 million lb, a 43% decrease from its release in 2001. Meanwhile, the releases

from 3,581 chemical manufacturing facilities accounted for 551.2 million lb, or about 12% of all discharges. Broken down by pathway, the chemical manufacturing industry (CMI) emitted 234.4 million lb, or 14.4% of the total air emissions. This was second only to the 694 electrical utility facilities that emitted 722.6 million lb of pollutants. The CMI released 56.7 million lb of pollutants to surface water (24.7%), whereas the food industry, with 1,695 facilities, released 68.9 million lb of pollutants to surface water (30%). With respect to underground injection, the CMI released 177.7 million lb of material, which accounted for 79.9% of the total 222.3 million lb disposed of in Class I–V injection wells.

Alaska reported the largest releases, totaling 548 million lb, with Nevada a close second at 499 million lb. Rounding out the top 10 states were AZ (329.3 million lb), TX (263.1 million lb), OH (253.9 million lb), IN (221.2 million lb), UT (174.9 million lb), PA (169.1 million lb), TN (156.1 million lb) and FL (154.6 million lb). Together, these 10 states accounted for 57.8% of the reported releases.

Onsite and offsite disposal or other releases for dioxin and dioxin-like compounds totaled 141,187 g in 2002 (excluding the error in reporting by one facility). Offsite disposal or other releases made up more than half of this amount, totaling up to

97.142 kg, or 62%. Onsite disposal or other releases were 38% or 54.045 kg. Air emissions were 4.909 kg. From 2001 to 2002, total on- and off-site disposal or other releases decreased by 5% (7.802 kg, excluding reporting by the facility with the error). An overall increase of 43% (42.188 kg) was reported from 2000 to 2002. The 43% increase resulted from reporting by two facilities, one in Texas that improved its release estimation techniques and another in Delaware reporting a one-time shutdown and closure of a process impoundment.

In filing their 2002 reports, over 10,000 TRI reporting facilities used EPA's interactive reporting software tool, called TRI Made Easy, or "TRI-ME," which assists facilities in completing their TRI obligations by simplifying and expediting reporting and improving data quality. The TRI data and background information are available to the public at [www.epa.gov/tri](http://www.epa.gov/tri) and the TRI explorer mapping tool is available at [www.epa.gov/triexplorer](http://www.epa.gov/triexplorer).

Note: Data are from TRI Form R, Section 5 (all parts) and Section 6.1 (metals and metal compounds only) and Section 6.2 (disposal codes only and metals and metal compounds reported under codes M40 and M61) as of April 2004. Offsite disposal or other releases transferred to other TRI facilities reporting such transfers as onsite disposal or other releases are not included.

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