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High-throughput path to acquisition

Drug delivery technologies generally leave a lot to be desired. Oral dosage doesn't work for large proteins, and injection is unpleasant for the patient and requires special attention from a physician. Skin-based delivery is a highly sought-after alternative. However, skin is a challenging barrier. Only a few transdermal drug delivery systems are available on the market, and they deliver only low-molecular-weight lipophilic drugs. Larger molecules such as proteins are a special challenge. The primary obstacle is low permeability through the lipid-rich matrix filled with nonviable skin cells that forms the outer layer of skin (the stratum corneum).

A large number of chemical penetration enhancers (CPEs) are known to disrupt the structure of this layer, including surfactants, fatty acids and fatty esters, but few actually improve drug transport. Moreover, those that do improve drug transport often must be used at high concentrations, increasing the odds that they will become an irritant. As a result, attempts to optimize individual enhancers usually require some compromise in safety. "You have to strike a balance," says Samir Mitragotri, professor of chemical engineering at the University of California at Santa Barbara.

Some attempts have been made to screen combinations of CPEs for synergistic effects that might improve transport at concentrations low enough to avoid irritation. The existence of hundreds of known CPEs calls for high-throughput screening techniques, as traditional screening methods are labor-intensive and time consuming. To get around these problems, Mitragotri developed a new strategy based on electrical impedance as a stand-in for molecular permeability, described in his 2004 paper in *Nature Biotechnology*[1]. A decrease in electrical impedance of the skin's surface suggests that drugs will also move more freely through the barrier. Mitragotri's technique measures the electrical impedance changes caused by application of various CPE combinations, eliminating the time-consuming sampling steps in other techniques. "It can be measured in a few seconds, and there's no need to transfer samples. All it needs is a pair of electrodes to measure the currents," Mitragotri says.

Since the paper was published, the technology has been licensed to fqubed, now a wholly-owned subsidiary of Nuvo Research (Mississauga, ON, Canada). The system, now branded 'INSIGHT', required some tweaking. "The first thing we had to do was take this development from its academic context and apply our engineering expertise to improve the robustness and reproducibility for use in routine industrial practice. That required several iterations of development," says John M. Newsam, president and managing director of fqubed.

The high-throughput experimentation technology has allowed the company to optimize the characteristics of lead formulations, simply by allowing fqubed researchers to screen a great many more formulations than would otherwise be possible. "Samir's technology also inspired us to develop other high-throughput experimentation methods of screening the effect of materials on various properties of skin," says Newsam. "We believe if we're doing a hundred times more measurements than someone else, then the prospective product will be better."

Newsam says that the INSIGHT system was a substantial factor behind the acquisition of fqubed by Nuvo Research in 2005. Initially, fqubed undertook contract research for Nuvo. "The (fast) pace of the program" helped convince Nuvo Research to make the acquisition, he says.

Mitragotri is continuing to use the system to study the mechanism of action of CPE. "It allows us to weed out formulations that we shouldn't spend time on—[and after that] we can perform really focused studies on leading hits using conventional tools," says Mitragotri.

Samir Mitragotri's high-throughput methods for screening chemical enhancer combinations made a licensee a valuable target for acquisition.

The work has produced some leads into mechanisms of synergy. "It's possible that the chemical enhancers interact in solution on the skin and then form a new chemical entity, or they may go in independently and work synergistically within the skin (barrier)," he says. In fact, experiments have provided evidence that both mechanisms may occur. "Hopefully in the near future we'll understand these mechanisms—but until then, screening is the only way to find these synergistic combinations," Mitragotri says.

1. Karande, P., Jain, A. & Mitragotri, S. Discovery of transdermal penetration enhancers by high-throughput screening *Nat. Biotechnol.* **22**, 192–197 (2004). (29 citations)