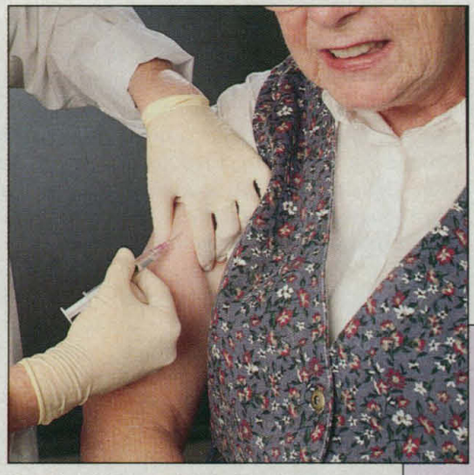
Drug Delivery Takes a Deep Breath

Medicines of the future, the fruits of today's biotechnology industry, may not require patients to face a shot in the arm. Instead they may need only inhale a fine powder or spray

While biotechnology is proving highly successful at getting new drugs onto the market, getting them into patients is another matter. With the help of new technologies for gene splicing and expression, companies continue to push dozens of new drugs into clinical trials each year, according to *Bioworld*, an industry watchdog. But a large number of these compounds are peptides and proteins, which are easily broken down by enzymes in the stomach; if they were taken as a pill, they would never make it to their destination. As a result, patients must brave an injection to take advantage of most of these new high-tech medicines. For potentially life-threatening diseases, that is rarely an impediment, but drug company executives worry that for other treatments the complication and expense of injection—not to mention needle phobia—will stunt sales and hurt their bottom line.



PHOTOS: INHALE THERAPEUTIC SYSTEMS

Special delivery. Inhalation devices *(right)* may free diabetics from a lifetime of insulin injections.

Looking for another way, drug companies around the world are now exploring the possibility of having patients inhale their medicine. Their hope is that tiny drug particles inhaled deeply into the lung will cross through the thin tissue lining into the bloodstream and then make their way to their intended destination. Such inhalable drugs "would be a huge boon" to the drug industry, says W. Leigh Thompson, a pharmacologist and consultant who recently retired as chief scientist of drug giant Eli Lilly & Co. in Indianapolis. And the hope is more than just a wistful dream. Clinical trials are already under way with inhalable formulations of currently marketed drugs, including insulin, morphine, and drugs to fight osteoporosis. Work on many more compounds remains in an earlier preclinical stage.

The new work is not the only alternative to injections being pursued. Industrial and academic researchers are also testing novel nasal sprays, skin patches, and even patches that dissolve when stuck to the gums. Nevertheless, many researchers seem particularly bullish about the new inhalable medications, in part because of their ease of use and steadily improving performance. "I think pulmonary delivery will emerge as the preferred route for some peptides and proteins," says David Kabakoff, the executive vice president of Dura Pharmaceuticals, a San Diego–based biotech company that produces respiratory drugs. "After all, the purpose of the lung is to exchange substances with the bloodstream," he says. Adds Thompson: "I think that it's the future."

But according to many industry observers, it is still too early for proponents of inhaled drug delivery, as well as hopeful patients, to breathe easily. It typically costs more to deliver the same dose of an inhaled drug than it does to inject it, as invariably only a fraction of inhaled drugs finds its way into the bloodstream as intended—the rest remains lodged in the delivery device or the patient's throat, where it is not absorbed. Any new scheme also must pass a host of safety and efficacy hurdles, so needles will not be disappearing anytime soon. Nevertheless, says Doris Wall, a drug-delivery expert with Bristol-Myers Squibb in New Brunswick, New Jersey, "People are watching [the field] with a whole lot of interest." Over the past couple of years, adds Kabakoff, "the field has moved from 'Can this work at all?' to 'Where is this going to be attractive clinically, medically, and economically?' "

A second wind

Inhaled drugs themselves are, of course, nothing new. Tobacco, marijuana, and opium are just a few of the compounds, legal or otherwise, that are smoked and inhaled so that their active components pass into the bloodstream. Asthmatics have long used inhalers to administer airway-opening compounds such as albuterol. And in 1994, Genentech began marketing the first aerosol-delivered protein, a recombinant form of the natural human enzyme deoxyribonuclease, which breaks down unwanted DNA that builds up in the lungs of patients suffering from cystic fibrosis. Genentech and other companies are now working on delivering other peptides, proteins, and small-drug molecules into the lung to work locally in treating respiratory diseases, such as cystic fibrosis and asthma.

But the broader and potentially more lucrative goal for many companies is to use the lungs simply as a route into the bloodstream. "It's a lot easier and more convenient to take a puff and get your drug" than to receive a shot, says Theresa Sweeney, a physiologist and pulmonary-delivery expert at Genentech in South San Francisco, California. The lung has an enormous surface area and an extremely thin tissue lining, both of which can make absorption of many drugs as fast as, or faster than, injecting them under the skin does. Lung tissue also seems to allow large molecules such as proteins to pass into the blood. Unlike the gut, there are few proteases present in the deep lung to break down the protein and peptide compounds.

Researchers have long known about most of these advantages. But the current devices for sending drugs to the lung, used primarily for asthma medications, are too inefficient at delivering their cargo to make them economically viable for more than a handful of products. These devices, called nebulizers (which deliver drugs in a water-based mist) and metered-dose inhalers (in which the drug is suspended in a propellant) only manage to get about 5% to 10% of the drug from the inhaler into the lung.

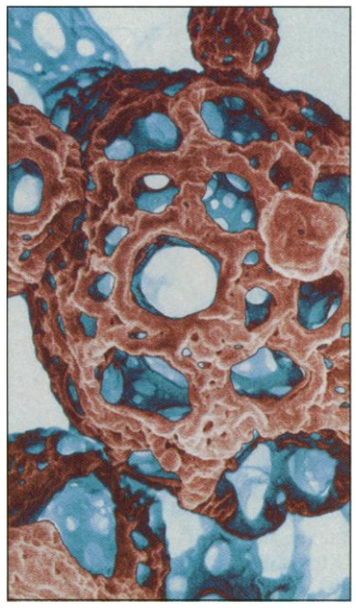
That is fine as long as the drugs are cheap to make, but not for expensive new peptide and protein drugs. One of the big problems with existing devices is that many rely on high-pressure propellants, which blast most of the drug directly into the back of a patient's throat, where it becomes lodged. Particle size is another challenge: They can either be too

small—below 1 micrometer in diameter—which causes them to stick together and interferes with their activity, or too large—above 5 micrometers—which means they are normally poor fliers and get stuck in the upper airways or the back of the throat.

In recent years, however, companies such as a trio of Californian firms—start-ups Inhale Therapeutic Systems of Palo Alto and Aradigm of Hayward, along with midsized Dura of San Diego—have come up with new delivery devices that they say better control particle size and increase the efficiency of delivery. Dura and Inhale both opted to deliver their drugs as fine powders rather than as tiny droplets of liquid. A premeasured dose is placed in a device that essentially blows the powder into a cloud of tiny particles, which is then inhaled with a slow breath deep into the lungs. Aradigm, meanwhile, has developed a new type of nebulizer that pushes a liquid formulation of a drug through an array of tiny holes, producing a mist of uniform, ultrafine droplets, which are then inhaled.

Besides improving devices, in recent years researchers have made considerable headway in new drug-formulation techniques to stabilize proteins into dry powders of the right size particles, says Richard DiMarchi, Eli Lilly's vice president for research technologies and proteins. Here too, however, companies such as Inhale are loath to divulge their secrets. "The technology has progressed to the point where people can contemplate this as a practical alternative," says Kabakoff. DiMarchi agrees: "I think the stars are appropriately aligned."

Many companies are betting that alignment will hold. Firms ranging from the likes of Inhale and Aradigm to giants such as Baxter, Boehringer Ingelheim, and Pfizer are either bankrolling or are themselves trying out lung delivery of everything from small molecules (such as morphine for cancer pain) to large proteins (such as antibodies to stem the allergic reactions that precede asthma attacks). But perhaps the biggest race is to develop inhalable insulin to treat diabetes. Today, more than 6.5 million people in the United States alone have been diagnosed with diabetes, about a quarter of whom must take daily injections of insulin, which allows the body to metabolize glucose. The current worldwide market for insulin, plus the needles and supplies needed to deliver it, is $2.9 billion and growing. And according to many, this area is ripe for a better alternative.



J. HRKACH, C. HALLBECK, S. HIROSUE, B. KRIWET/MIT

Great balls of insulin. Biodegradable polymers could ferry drugs to the lungs.

Many diabetics inject themselves as often as four times daily, which can be difficult, especially for small children. And some insulin regimes rely on a slow-acting, long-lived formulation, so that meals must be taken at the right time and be of the right size—otherwise, patients risk dangerous fluctuations in their blood glucose levels.

Bated breath

Now teams at Inhale and Aradigm are racing to come out with an inhalable form of insulin, each using their own drug formulation and both claiming that their techniques produce the right-sized drug particles and high-efficiency delivery. Inhale combines the insulin with sugar molecules to make an ultrafine powder that works in the company's delivery device. Just prior to delivery, the blast of compressed air forces the powder through a nozzle, which breaks clumps apart into a trapped cloud of individual particles that the patient then breathes in. Aradigm officials say that the key to their rival, liquid-based technology is a cheap way to make disposable arrays of tiny, 1-micrometer-sized nozzles. The disposable nozzles are needed because protein molecules can get trapped in the tiny nozzles and interfere with their ability to create uniform droplets roughly 3 micrometers across.

As for the exact efficiency of delivering insulin to the lung, both companies say that information remains proprietary. But according to several industry watchers, the new inhaler systems can consistently deliver 20% to 50% of their medicine to the lung. And Inhale's research director John Patton says Inhale's early clinical trials have shown that the insulin that does make it to the deep lung is absorbed quickly and is released into the bloodstream in a manner that is "very close to the natural release profile from a healthy pancreas," the organ that normally produces insulin. Aradigm's efforts remain in the preclinical stage in the United States, but the company has carried out early-stage human trials in Australia.

Any insulin-delivery system also has to administer precisely the right dose, because diabetics must be able to know how much food they need to balance the insulin, notes DiMarchi of Eli Lilly, one of the world's largest marketers of the substance. Both Aradigm and Inhale tightly control how much insulin is delivered with their devices—Inhale, by placing the compound in premeasured doses that are loaded into the inhaler; and Aradigm with electronic controls that monitor delivered dosage and the patient's breathing. While full clinical trials remain to be done, Thompson says that from what he has seen of Aradigm's delivery system at least, the doses it delivers are no more variable than those from different subcutaneous injections.

Inhalable insulin has other hurdles to jump, however: DiMarchi points out that, although insulin's market is large, the profit margins on selling the drug are rather small. Most diabetics, he says, currently pay only about $1 a day for their medication. That means an inhalable formulation will likely need to be priced similarly. That could be a problem, particularly if the devices deliver only 20% to 50% of their drug cargo to the lungs and then only a fraction of that is absorbed into the bloodstream. Finally, he adds, Inhale's current clinical trials only involve the form of insulin intended to be taken before meals. Many diabetics inject another longer lived form, known as basal insulin, before sleep to regulate glucose levels through the night.

But recent research may provide a solution here as well. In the 20 June issue of *Science* (p. 1868), David Edwards and his colleagues at Pennsylvania State University, the Massachusetts Institute of Technology, and the Israel Institute of Technology reported creating time-release, inhalable formulations of insulin and other drugs that were effective over a period of days. Edwards and his colleagues incorporated insulin into large—8 to 20 micrometers—porous, spherical particles made from a biodegradable polymer. Then they administered them to rats with an inhaler.

Even though these particles are larger than those that prevailing wisdom says work best, Edwards and his colleagues found that the spheres' light and hollow core allowed them to fly deep into the lungs. Once there, the polymer's slow degradation released the insulin steadily over a period of 96 hours. The new work "was quite an interesting approach," says Anthony J. Hickey, an aerosol-delivery expert at the University of North Carolina, Chapel Hill, and underscores the fact that there is still plenty of room for improving current airway-delivery systems.

That message is not lost on those trying to commercialize the technology. "I think it's really exciting, all the potential [inhalable] drugs that are on the horizon," says Genentech's Sweeney. Chances are that most will not pan out, but if some of them do, she adds, "that will have a big impact on how we think about delivering drugs."

–Robert F. Service