Improving the

Asthma Arsenal

A new method for depositing nanometer-thin coatings onto tiny particles could be used for a wide range of industrial applications, including making safer and more convenient asthma drugs, say the scientists who developed it. Colleagues Rajiv Singh, a professor in the Department of Materials Science and Engineering at the University of Florida in Gainesville; Guenther Hochhaus and James Talton, an associate professor and postdoctoral associate, respectively, in the university’s Department of Pharmaceutics; and James Fitz-Gerald of the Naval Research Laboratory in Washington, DC, have begun using the new technique—pulse laser deposition—to coat glucocorticoids with thin layers of a biodegradable polymer.

Glucocorticoids are the strongest and longest-lasting asthma treatment in use today. They are used to reduce inflammation in the lungs of many asthma patients, but once the drugs are absorbed into the bloodstream, they become ineffective. Recent studies have also suggested that high concentrations of glucocorticoids in the blood may inhibit growth in children by obstructing the body’s normal hormone production. The hope is that coating these inhaled steroids will reduce the concentrations that collect in the blood of asthma patients.

Coat of Many Colors

“What we have developed is a very fast process that applies a thin coating of a polymer to the steroid but essentially doesn’t change the size of the inhaled particle,” says Talton. Because the coating, known as poly(lactic-co-glycolic) acid (PLGA) dissolves slowly, it provides longer sustained release of the drug, says Talton. Keeping the steroid in the lungs longer means less is absorbed systemically, and this means fewer side effects.

The method is especially appealing because it gives researchers great flexibility in selecting what particles they use and the properties of the coatings they apply. “Most of the coating techniques that have been around, especially in the pharmaceutical area . . . are very, very specific to the type of material you use,” explains Singh. “The nice thing about this process is it’s more universal. You can take almost any particle, A, and almost any coating, B, and put a coating of B on A . . . You can even dial in the thickness of the coating that you need.”

The method is still in its infancy, and years of study and testing will be necessary before the drug coating technique can be used in asthma inhalers. “This has the potential to be a very exciting advance in aerosol asthma medication,” says David Peden, director of the Pediatric Asthma Program at the University of North Carolina at Chapel Hill, “but like all advances, it bears confirmation with both animal and, eventually, human studies.”

Pulsing Particles

The basic pulse laser technique was developed by Singh and Fitz-Gerald at the Engineering Research Center for Particle Science and Technology at the University of Florida, a laboratory established by the National Science Foundation. “We were looking for a new coating technique to coat any material—polymeric materials, ceramics, or metals—onto particles,” says Singh.

The method they arrived at employs a high-intensity laser to heat the coating substance, producing a supersonic shock wave of the heated material called a plume. The plume is produced inside a vacuum chamber containing particles of the substance to be coated. “We shoot a laser into that chamber to create a flux [or flow] of the coating material,” says Singh. “The coating material is then ready to condense on any surface it [contacts], so it condenses on the drug particles or whatever particles are in the chamber.” Recently, the technique was used by a team led by Fitz-Gerald to apply 20–30-nanometer coatings of...
silver and rare earth metals to particles of alumina and silica. The results of that work appeared in the Journal of Materials Research in August 1999.

Research on the use of pulse laser deposition for asthma drugs has yet to be published, but initial data presented at the Fall 1998 meeting of the Materials Research Society suggested that rats retain coated glucocorticoids in their lungs much longer than uncoated glucocorticoids. The half-life of the coated drugs in the lungs was found to be about one hour, compared to just over a minute for the uncoated drugs. That suggests that concentrations in the blood would be lower with the coated drug, which would reduce the risk of adverse side effects. And, says Singh, because the polymer coating is very thin—often less than 0.1% of the whole coated particle—there is very little concern that adverse effects from accumulation of the polymer in the lungs would be seen.

As an added benefit, the drug's longer retention time and slower release rate in the lungs mean that it could probably be used less frequently. "With this system you can basically tailor whatever release rate you want, for an hour or two up to a couple of days," says Talton. "Any time you have to use a drug less often," says Peden, "the chances are higher that people will continue using it [on the correct schedule]."

**Improved Inhalers**

Glucocorticoids are delivered to patients through inhalers to maximize the action of the drug on inflamed cells in the lungs, though the steroids are also sometimes given orally to patients with severe asthma. "If they're given [orally] or at really high doses through inhalation, enough may get into the bloodstream to inhibit the adrenal gland from producing endogenous steroids," says Darryl Zeldin, head of the Clinical Studies Section of the Laboratory of Pulmonary Pathobiology at the NIEHS. "The body sees the exogenous steroids and it thinks it doesn't need to produce endogenous ones that are important for a number of biological processes." In children, when the production of some steroids slows, growth may not proceed at the normal rate.

There are also other potential side effects of glucocorticoids that are a concern in both adults and children, says Peden. The drugs have been associated with changes in the eye, including cataracts, and they can suppress the immune system. However, says Zeldin, "The systemic side effects of inhaled steroids shouldn't be overstated. ... In most cases, they are really amazing safe drugs."

Still, concern over growth-related side effects of inhaled corticosteroids (of which glucocorticoids are a subset) led the Food and Drug Administration to convene an expert panel in July 1998 to discuss their continued use in children, who account for about one-third of all asthma patients. The conclusion of that panel was that not enough evidence of developmental problems in children exists to warrant any reduction in the use of the drugs. However, the panel said that such side effects need to be studied further, and it recommended that physicians monitor the growth of all children to whom they prescribe the inhaled steroids.

Recognizing subtle abnormalities in the growth of children is difficult, though, and Peden says asthma itself may cause slight changes in growth rate, making such effects even more difficult to identify. Therefore, it may be a long time before scientists are able to accurately describe the risks associated with these asthma treatments.

The debate over the safety of corticosteroids has not gone unnoticed by the parents of some asthmatic children. "They often just don't like the notion of their children being on steroids in the first place," says Peden, "and whether they are really aware of the effects on growth or have just heard the general buzz ... they may be more reluctant to give these treatments to their children." That can be dangerous because severe asthma attacks can be fatal. Also, other asthma drugs are generally not as effective as glucocorticoids at treating the disease.

"If you could reduce the systemic absorption of these drugs—at any level—that would be good," Peden says. Furthermore, he says, convincing users that the risk of such absorption has been eliminated would assuage some of their reluctance to use glucocorticoid asthma inhalers. That would likely result in less morbidity due to asthma, Peden says.

In the meantime, many other new drugs are being developed that attack asthma inflammation in other ways and avoid some of the potential risks associated with steroids. But thus far nothing as effective as glucocorticoids is available. "Steroids are certainly the mainstay of asthma therapy right now," Zeldin says, "and they will probably continue to be a mainstay in the future."

If the Florida researchers are correct, it may be possible to make steroids safer, thereby eliminating at least some of the need for new drugs. While Hochhaus concedes that the coating technique would add to the production costs of glucocorticoid drugs, he says, "It would probably not increase it too much. Compared to developing a new drug—a new chemical entity—it wouldn't be more expensive than that." Keeping costs low could be especially important when producing asthma therapies because the ailment is known to disproportionately affect the poor.

**Ongoing Research**

There is some reason to think that the PLGA coating will not be a panacea for all the problems with glucocorticoid asthma drugs. Peden points out that often a large portion of the inhaled asthma drug that enters the bloodstream does not reach the lungs but travels through the gastrointestinal tract. "Sometimes the majority of what comes out of the metered-dose inhaler is swallowed rather than inhaled," he says. There is little at this point to suggest that the new coatings would reduce systemic absorption through this path as well.

However, if the coating does turn out to be effective, Peden envisions other pharmaceutical uses for it, such as in delivery systems for inhalated antibiotics and for human immunodeficiency virus treatments. The researchers are also looking at uses outside the pharmaceutics industry. Singh says that manufacturers of flat panel displays have shown interest in the process for coating phosphorus particles, for example.

As for asthma treatments, Hochhaus cautions that this application is still in early development. Patent applications were filed only recently, and clinical trials are still 5–6 years away, he says. Says Zeldin, "It's a novel approach, but it remains to be seen whether it will turn out to be important."

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**Suggested Reading**

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