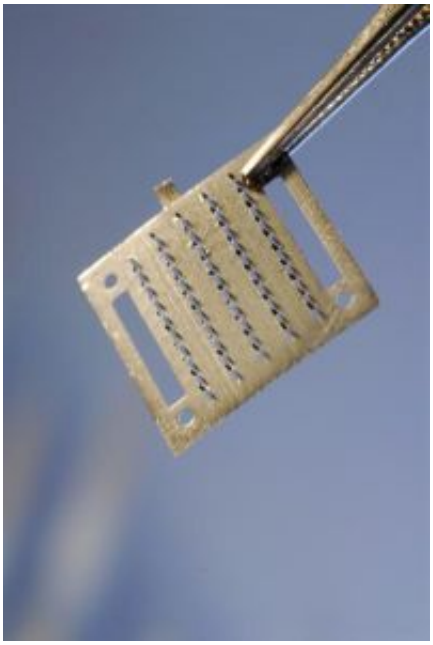
Microneedles enhance drug administration through skin

February 4 2008



Microscopic needle transdermal patch. Credit: Courtesy of Georgia Institute of Technology

In what is believed to be the first peer-reviewed study of its kind involving human subjects, researchers at the University of Kentucky College of Pharmacy and the Georgia Institute of Technology have demonstrated that patches coated on one side with microscopic needles can facilitate transdermal delivery of clinically-relevant doses of a drug that normally cannot pass through the skin.

Reported in the journal *Proceedings of the National Academy of Sciences*, the study could help advance the use of microneedles as a painless method for delivering drugs, proteins, DNA and vaccines into the body. The research also found other advantages for the microneedles, including an ability to produce therapeutic drug levels with lower doses, and lowered production of metabolites that may cause side-effects.

“This proof-of-concept study shows that microneedles work in humans for transdermal drug delivery,” said Daniel Wermeling, associate professor in the Department of Pharmacy Practice and Science at UK's College of Pharmacy. “Success with microneedles could cause us to rethink the convergence of the drug and delivery system and lead to a more integrated approach merging engineering with pharmaceutical technology.”

The research was supported by the National Institutes of Health and the University of Kentucky Research Foundation.

“This study represents an important landmark in the development of microneedles into drug delivery devices suitable for use in clinical medicine,” said Mark Prausnitz, a professor in the School of Chemical and Biomolecular Engineering at the Georgia Institute of Technology. “This method may be useful for a broad range of drugs that cannot normally be delivered without a hypodermic needle.”

Transdermal drug delivery has proven successful in a number of applications, including pain management, congestive heart failure and hormone replacement. Transdermal administration offers advantages over other delivery techniques, but existing systems can only be used for a narrow range of compounds that easily pass through the skin.

By painlessly punching a series of microscopic holes in the outer layer of skin known as the stratum corneum, microneedles promise to expand the

range of drugs and vaccines that can be delivered transdermally. Until this study, however, the only published research demonstrating drug delivery using microneedles had involved studies in animals and on human cadaver skin.

Working with Prausnitz and his Georgia Tech research team, Wermeling and colleagues Stan Banks, a graduate student in the UK College of Pharmacy Department of Pharmaceutical Sciences, David Hudson, fellow in the UK College of Medicine's Department of Psychiatry, and Audra Stinchcomb, associate professor in the UK Department of Pharmaceutical Sciences and co-author of the paper, set out to determine whether microneedle patches could indeed help deliver useful amounts of drug compounds that otherwise couldn't pass through the skin. As a test compound, they chose the drug naltrexone, a skin-impermeable compound that is used to treat opiate and alcohol addiction.

Working with a small group of non-addicted human test subjects, they first prepared a section of skin on each subject's arm by pressing and removing thumb-sized patches that contained 50 stainless steel microneedles each about 620 microns – about 1/40th of an inch – in length. Next, gel containing naltrexone was applied to the prepared area, which was then covered by a protective dressing.

The concentration of the drug in each subjects' bloodstream was monitored for 72 hours. The researchers quickly saw levels of the drug reach pharmacologically active concentrations, and those levels remained steady for at least 48 hours in the six test subjects.

Control subjects were treated in the same way, but without the microneedle preparation prior to application of the naltrexone gel. None of the control subjects had detectable levels of the drug in their bloodstream.

As part of the study, electrical resistance testing of the skin was done on separate subjects to determine how long the pores created by the microneedles remained open. Those tests suggested the drug could pass through treated skin for at least 48 hours before natural healing processes closed up the tiny punctures.

Beyond maintaining a steady level of the naltrexone, microneedle delivery may offer another advantage over oral administration: a reduction in the presence of compounds metabolized from the drug. The primary metabolite, known as naltrexol, is rapidly produced by the liver and intestines when the drug is administered orally, creating blood levels as much at ten times that of the parent drug – which can cause undesirable side effects. With microneedle administration, however, the levels of naltrexol stayed well below those of the naltrexone.

“During the first week of treatment using oral naltrexone, 10 to 20 percent of patients drop out of treatment because of side effects,” Wermeling said. “If you can change the way the parent drug is presented in a way that affects how the metabolites are formed, you could improve the safety or side effects of the drug.”

Microneedle administration also reduced the amount of drug required to produce therapeutic levels, replacing a 50 milligram tablet with 10-12 milligrams of drug in the gel. Use of the microneedles also produced steady bloodstream levels of the drug, without the initial peak that occurs with oral delivery.

The study represents a first step in demonstrating the broad range of potential uses for microneedles, said Prausnitz, who has been developing the devices for more than ten years. In addition to Prausnitz, the Georgia Tech research team also included Harvinder Gill and Jyoti Gupta.

“There are a number of ways in which microneedles can be used,”

Prausnitz noted. “This study addressed the simplest use of microneedles in which the needles are just inserted and removed from the skin and a drug patch applied. To understand how broadly microneedles can be used in medicine, we will also need to study delivery of other therapeutics, such as lidocaine, insulin and flu vaccine.”

The study has special significance for researcher and co-author Stan Banks. The work is the capstone of his thesis, and represents four years of preclinical studies with naltrexone and delivery systems under an NIH grant to Stinchcomb.

Source: University of Kentucky