Since the first transdermal patch was approved by the US Food and Drug Administration in 1979 to treat motion sickness, patches have become a useful means of delivering drugs for a number of purposes. Still, the barrier properties of the skin mean that currently only modest doses of small, lipophilic drugs can be effectively delivered through the skin.

But new research reported by scientists at the University of California, Santa Barbara, demonstrates that specially designed “chemical permeation enhancers” can be developed to potentially and safely permeate the skin so that a wider range of drugs might be administered transdermally. This means of enhancing topical drug delivery could enable physicians and patients to bypass the injected or oral forms of many drugs, along with some of their adverse effects.

**PERMEATING THE SKIN**

Researchers have experimented with a broad range of chemical additives that can enhance transdermal penetration. Such chemical permeation enhancers change the structure of the stratum corneum, the protective top layer of the skin, by removing or disorganizing lipids or by interacting with proteins. Unfortunately, the concentration of enhancers necessary to induce a sufficient change often causes skin irritation as well, usually as a consequence of the unfolding of proteins within skin cells.

To address this bothersome effect, the researchers set out to design permeation enhancers that could successfully permeate the skin without causing irritation. Their report demonstrates that certain techniques may be used to broaden the repertoire of chemicals that provide optimized transdermal drug delivery (Karande et al. Proc Natl Acad Sci U S A. 2005;102:4688-4693).

The study’s principal investigator, Samir Mitragotri, PhD, a chemical engineer, and colleagues used various methods to accomplish their task. First, they analyzed just how irritating a currently available chemical permeation enhancer is when it is applied to the skin and used spectroscopy to analyze the changes involved in enhancing permeability and causing irritation. Then, they performed molecular modeling to determine which physical properties of the chemical permeation enhancer are responsible for these changes.

When all of these data are taken together, the researchers hope to be able to look at the structure of any chemical and predict its effects on the skin, said Mitragotri. “And once we know these chemical rules, then our job becomes very easy, because then we can just draw a chemical structure on the computer and predict how will it behave with a change of one functional group here or there.” Mitragotri added that his team can take such chemical changes that produce different variants of a particular chemical permeation enhancer and screen them in a fraction of a second to find which variant has the greatest therapeutic potential.

The researchers looked at more than 100 currently available permeation enhancers and started altering them. “If you look at the total number of chemicals around and then all of the [changes] that can be done, we’re talking millions and even billions of molecules,” said Mitragotri. His team has barely scratched the surface, as it has designed approximately 325 permeation enhancers that have been screened on the computer and tested in vitro for molecular delivery.

The scientists found that potency and irritation do not necessarily go hand in hand in all permeation enhancers. “In some chemicals, they are fundamentally correlated, and in [others] they aren’t,” said Mitragotri. “Prior to our study, this wasn’t known.” Therefore, it makes sense to explore enhancers that exhibit strong potency but little skin irritation. The group has designed several new permeation enhancers whose chemical properties suggest that the candidates are both safe and effective.

**NEXT STEPS**

The transdermal patch is a convenient mode of drug delivery, demonstrated by patches currently used for a variety of purposes such as hormone replacement, contraception, and smoking cessation. The longest-lasting single patch can deliver a drug for about 1 week. In addition, to stop delivery, one can simply peel the patch off.

For Mitragotri, the next step is to broaden the number of chemicals to be screened to discover even more potent and safer chemical permeation enhancers. He then hopes to take those chemicals to the next level by using them to facilitate the delivery of specific drugs to animals.