Novel polymer helps oral medications reach the bloodstream

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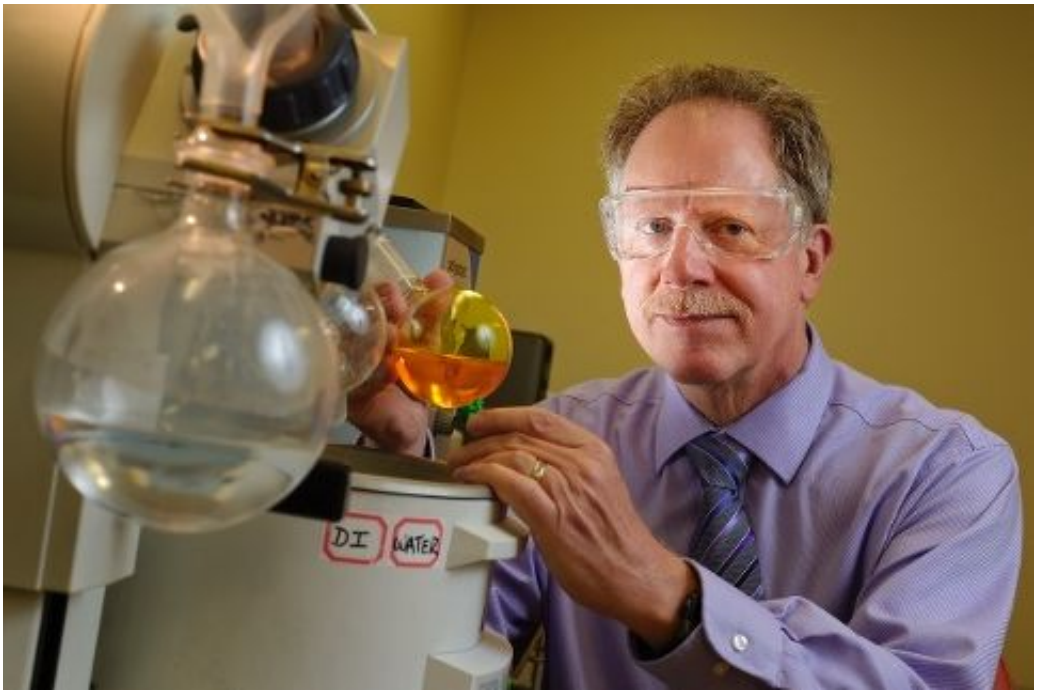

Kevin Edgar.

All too often, when a person takes a pill full of a potent and effective drug, the drug passes straight through the body, not reaching the organ where it is needed—a waste of money and inconvenient if it is a cold medicine, but potentially dire if it is a treatment for a serious illness. Polymer chemists at Virginia Tech and pharmaceutical scientists at Purdue University have teamed up to design a solution.

Their research to identify, understand, and create new polymer additives that enhance the ability of orally administered drugs to reach the bloodstream has been published in a series of journals. In a special issue of the Elsevier journal *Carbohydrate Polymers*, they introduced an all-natural polymer that can be used with a range of medicines to prevent crystallization during transport and storage; it then traverses the digestive tract until the still fully potent medicine is released from the polymer in the small intestine, where it is best absorbed into the bloodstream.

Kevin Edgar, professor of biomaterials and bioprocessing in the College of Natural Resources and Environment at Virginia Tech, an expert in polymer synthesis, approached Lynne Taylor, professor of industrial and physical pharmacy at Purdue University, about collaboration.

"Dr. Taylor is one of the leading pharmaceutical scientists in the world," said Edgar. "We decided that by combining her ability to understand how drugs, polymers, and the human body interact, with our ability to make new polymers based on natural, renewable polysaccharides, we could address the challenge of making some very important drugs more bioavailable through the creation of polymers tailor-made for this purpose."

Many important drugs are like table salt; they crystallize easily. When they do, the crystals are stubbornly difficult to dissolve. They crystallize instead of remaining dispersed, whether in the pill or after release in the digestive tract. Many medicines locked into crystals don't dissolve fast enough to work properly. If that happens, they can't reach their target.

Polymers are introduced to interfere with crystallization. "But the polymers that are presently FDA approved are not effective in meeting all the challenges," said Edgar. "They may prevent a process called nucleation but not stop growth of the crystal if it gets started. Or they may not continue to work after a period of time or if conditions are too

hot or too damp. We needed to design a better polymer."

Imagine sugar dissolved in water. If a bit of dust is introduced, it can lead to nucleation—the sugar sticks to the dust—and then crystal growth. In this example, the polymer would cover the dust mote and repel the sugar molecules, preventing nucleation.

"Stopping nucleation is relatively easy, like stopping a skier before he starts down the hill," said Edgar. "Stopping growth is harder, like trying to stop the skier once he is speeding down the slope. But our polymers can do both—stop nucleation and growth."

Edgar and Taylor are working with natural cellulose to create derivatives known as cellulose esters. "They are the polymers used to create LCD screens, automotive paint, and cellophane tape," said Edgar. "Cellulose is an abundant, renewable, completely natural polymer used by nature as the 'steel reinforcing rod' of trees and a major component of all plants."

The Virginia Tech and Purdue groups have discovered that the effective design for pharmaceutical applications is cellulose omega-carboxyesters, which are cellulose esters that the researchers have enhanced with acids that already occur in the human body.

"For example, adipic acid, a natural acid present in sugar cane, can be attached to cellulose acetate to make an adipate ester," said Edgar. "Cellulose acetate is already used in many medicines that people take today; it controls the rate of release of the drug."

The researchers figured out how to make omega-carboxyesters that keep different kinds of medicines dispersed and prevent them from crystallizing—in other words, creating pills with higher bioavailability.

"No polymers work in every drug formulation, but these are some of the

most broadly effective bioavailability enhancement polymers we've seen." said Edgar. "We have already found that they enhance the stability and solubility of three HIV drugs, a pain reliever, two antibiotics, and five flavonoids, which are potent drug-like molecules that occur naturally in nuts, fruits, and vegetables."

The final neat trick, after creating a polymer that binds the medicines so they cannot crystallize, is to make sure that polymer also knows when to let go.

"The small intestine is where many medicines have the best chance to enter the bloodstream," said Taylor, "so often the ideal polymer will hang onto the drug through the acidic environment of the stomach, and then release the medicine in the benign environment of the small intestine."

Cellulose adipate esters and their cousin omega-carboxyester, cellulose acetate suberate, are no more complicated to make than those in adhesive tape and other inexpensive products, except that they are made with a different set of natural acids.

"Most of the cellulose omega-carboxyester just passes through the body unchanged and unabsorbed. If any of it breaks down in the gastrointestinal tract, it breaks down into things that are part of our diet anyway," said Edgar.

"We are excited by these compounds, and there are companies interested in making the investments to get them approved," Edgar added.

The article in *Carbohydrate Polymers*, "Synthesis and structure-property evaluation of cellulose omega-carboxyesters for amorphous solid dispersions," describes the successful use of the novel polymers with the anti-HIV drug ritonavir.

An article in the April 18, 2013, American Chemical Society journal *Molecular Pharmaceutics* described how a group of chemically diverse polymers worked to stabilize three structurally different medicines: ritonavir and efavirenz, both used for treating HIV, and celecoxib, used for treatment of arthritis and other painful inflammations. The article "Impact of polymers of crystal growth rate of structurally diverse compounds from aqueous solution" was authored by Ilevbare, Liu, Edgar, and Taylor.

The group had previously published research examining a range of commercially available and novel polymers used with ritonavir; resveratrol, which is the beneficial compound in chocolate and red wine; and ellagic acid, the flavonoid in walnuts and many kinds of berries that acts against oxidation-related chronic diseases, such as cancer and cardiovascular disease. Their work continues with other drugs, including important antibacterial drugs such as those used against tuberculosis.

"Improved bioavailability means a scarce and expensive drug can be used to treat more patients and with fewer side effects," said Taylor. "Fewer doses will be required, overall making it easier for patients to take their drugs on time every day—nothing is more important for vanquishing disease and for preventing the development of resistant organisms."

More information: www.sciencedirect.com/science/ … ii/S0144861712011629

Provided by Virginia Tech

https://phys.org/news/2013-08-polymer-oral-medications-bloodstream.html