Ultra-long acting pill offers new hope in eliminating malaria

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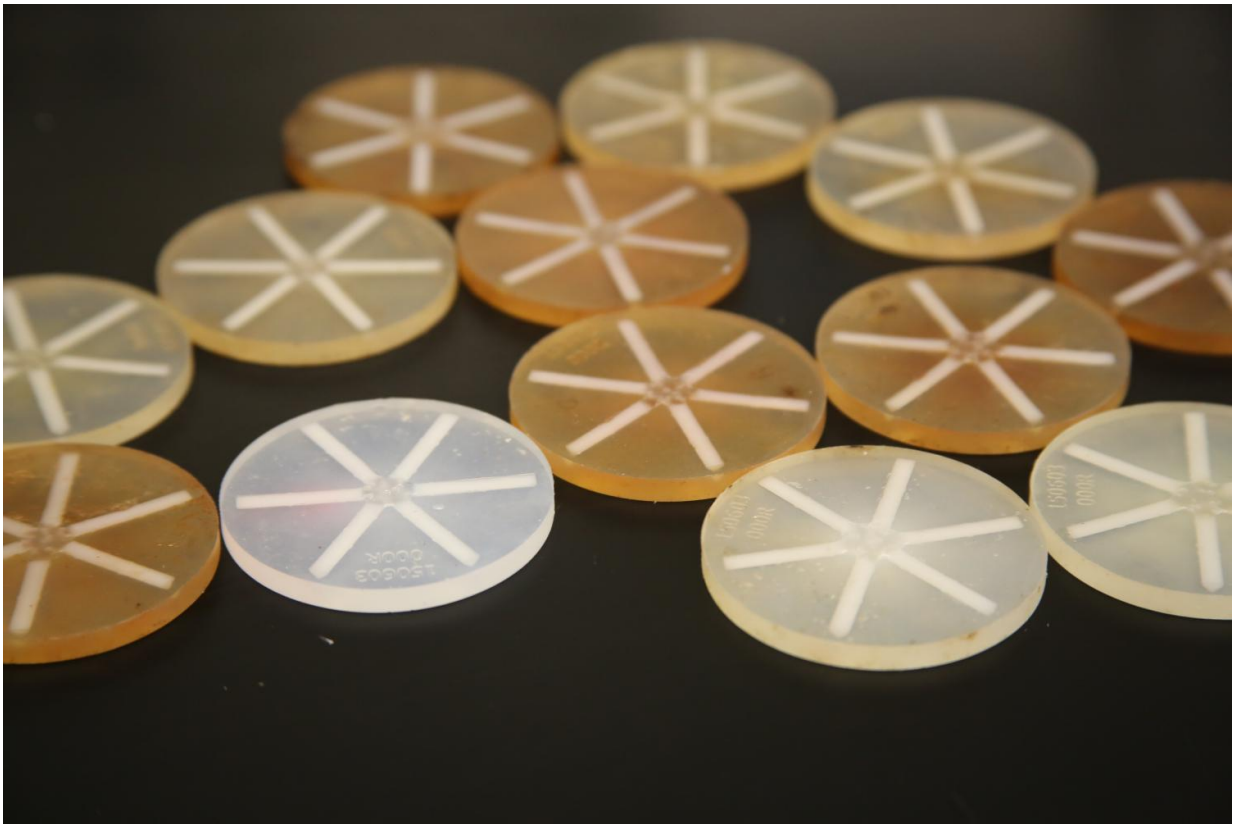

Prototype dosage forms being molded in silicone molds. Credit: Brigham and Women's Hopsital's Communication & Public Affairs

Imagine swallowing a pill today that continues releasing the daily dose of a medicine you need for the next week, month or even longer.

Investigators from Brigham and Women's Hospital and their collaborators from the Massachusetts Institute of Technology have developed a long-acting drug delivery capsule that may help to do just that in the future. To test the capsule's real-world applications, the team used both mathematical modeling and animal models to investigate the effects of delivering a sustained therapeutic dose of a drug called ivermectin, which is used to treat parasitic infections such as river blindness. Ivermectin has an added bonus of helping keep malaria-carrying mosquito populations at bay. The team found that in large animal models, the capsule safely stayed in the stomach, slowly releasing the drug for up to 14 days, and potentially providing a new way to combat malaria and other infectious diseases.

The results of this work are published Nov. 16 in *Science Translational Medicine*.

"We want to make it as easy as possible for people to take their medications over a sustained period of time. When patients have to remember to take a drug everyday or multiple times a day, we start to see less and less adherence to the regimen. Being able to swallow a capsule once a week or once a month could change the way we think about delivering medications," said co-corresponding author C. Giovanni Traverso, MB, BChir, PhD, a gastroenterologist and biomedical engineer in the Division of Gastroenterology at BWH and an instructor of medicine at Harvard Medical School.

Medication non-adherence is a massive problem in the U.S. and globally. In the U.S. alone, non-adherence is estimated to lead to more than $100 billion in expenses annually. Medication non-adherence is also a persistent problem in low-resource settings, where there may not be reliable access to health care and the full course of a medication. To help develop a new solution, the multi-disciplinary research team included members with expertise in biomechanical engineering, pharmaceutical

sciences, infectious disease modeling, polymer chemistry and health care innovation.

"In addition to improving adherence, our ultra long-acting drug delivery system may reduce side effects and improve drug efficacy by smoothing out the high variability of serum concentration that often comes with taking a daily pill," said co-first Andrew Bellinger, MD, PhD, a cardiologist at BWH and co-founder and chief scientific officer at Lyndra, the healthcare company that licensed the technology from MIT and BWH and is developing it for commercial use in the U.S. and worldwide. The company is focusing on drug delivery for neuropsychiatric disorders. (Other diseases that could benefit from ultra long-lasting drug delivery include tuberculosis, HIV, diabetes, and epilepsy.)

The research team developed a capsule that is about the size of a fish oil capsule when swallowed. Once inside the stomach, the capsule unfolds into a star-shaped structure too large to pass through the pylorus and exit the stomach, but designed to allow food to continue passing through the digestive system.

"The gastrointestinal tract is a strong, durable passage way through the body. We designed the capsule to pause its transit in the stomach to allow for more controlled drug delivery and absorption, before passing through the GI tract without any harm," said Traverso. "Some of the challenges we face in getting the capsule in place are the 'ship in the bottle problem' - in this case, the neck of the bottle is the esophagus - and preventing the capsule from passing through the rest of the tube. The pylorus is about 2 centimeters in diameter so we designed our system to be 4 centimeters when it opens."

The capsule contains polymers and other materials mixed with ivermectin to allow the drug to slowly diffuse out of the material over

time. The team reports evidence of diffusion for up to two weeks, and is interested in continuing to develop the system so that it can provide the drug for one month or longer.

Ivermectin is currently used to combat several kinds of parasites, including the parasitic worms that causes river blindness and lymphatic filariasis. (The researchers who discovered ivermectin were awarded the Nobel prize in 2015.) Ivermectin has also been shown to reduce malaria transmission as the drug is toxic to the mosquito species that spread malaria (Anopheles). The concentrations of ivermectin in the blood of humans taking the drug are high enough to kill mosquitoes that bite them.

In collaboration with research teams at Imperial College London and the Institute of Disease Modeling in Seattle, the team applied mathematical modeling of malaria transmission and found that long-lasting ivermectin levels could amplify the efficacy towards malaria elimination of mass drug administration campaigns.

In addition, they envision potential applications beyond infectious disease, including chronic diseases such as psychiatric disease, heart disease, renal disease and more. They plan to investigate the system's applications for these conditions as well.

More information: Bellinger AM et al. "Oral, ultra-long-lasting drug delivery: Application toward malaria elimination goals." *Science Translational Medicine* DOI: 10.1126/scitranslmed.aag2374

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