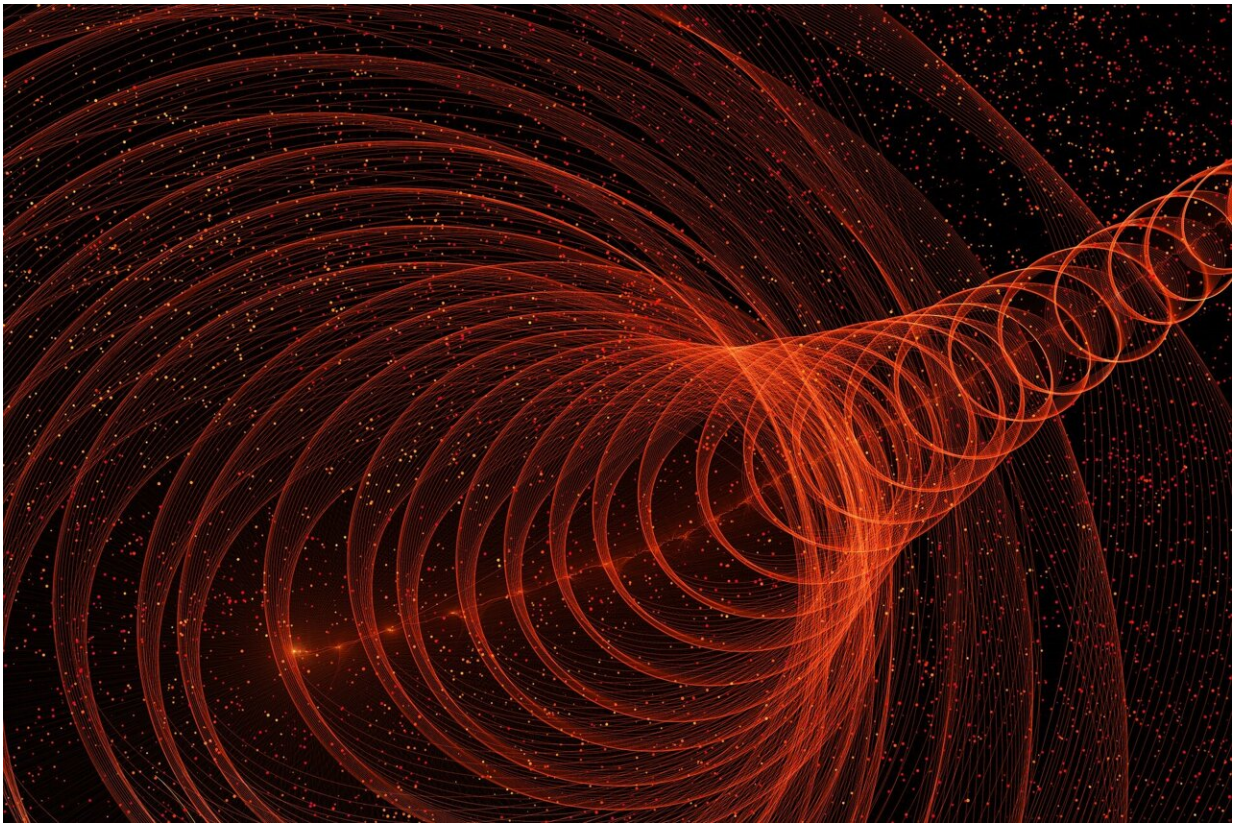


Ultrasound beam triggers 'nanodroplets' to deliver drugs at exactly the right spot

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Conventional drug delivery is often like cracking a nut with a sledgehammer. Whether the drug is swallowed, injected, inhaled, or absorbed through the skin, it ultimately diffuses to most parts of the

body, including those where it isn't needed—or where it might even cause harm.

But what if the delivery could be targeted at exactly the right spot? This would allow the total dose to be dramatically lower, thus minimizing side-effects.

Now, scientists from the US have found a way to perfect a promising, emerging method that does just that. With their new protocol, the method is made both safe and efficient for the first time, hopefully paving the way for first-in-human trials. The results are [published](#) in *Frontiers in Molecular Biosciences*.

"Here we show a method to deliver drugs to specific areas of the body where they are needed. We do so using [ultrasound waves](#), which trigger drug release from circulating nanocarriers when focused on the target," said Matthew G Wilson, a graduate research assistant at the University of Utah, and the study's first author. "We developed a method to produce stable nanocarriers repeatably, and identified [ultrasound](#) parameters that can activate them."

Nanoengineered droplets

The nanocarriers are minuscule droplets, between 470 and 550 nanometers across, with a hollow outer shell composed of polymer molecules. These polymers have two distinct ends: a hydrophilic one, which mixes well with watery solutions like blood and which faces outward, and a hydrophobic one that doesn't mix with water and which faces inwards.

Within the shell is an inner core of hydrophobic perfluorocarbons, molecules that consist mostly of fluorine and carbon, and that are mixed with an equally hydrophobic drug of interest. The shells keep the cores

apart, preventing them from coalescing into a single droplet, and form a barrier against the immune system. The effect is much like mayonnaise, where proteins from eggs form droplets of encapsulated oils, where otherwise the oil and water would separate completely.

To release the drug, the researchers played back an ultrasound—a [sound wave](#) with a frequency beyond the upper limit of human hearing—of 300 or 900 kilohertz. The beam of ultrasound can be steered across three dimensions, to focus on a desired area within the body that is only a few millimeters across.

The ultrasound is thought to cause the perfluorocarbons to expand, stretching out the droplet's shell and making it more permeable to the drug, which then diffuses out to the organs, tissues, or cells where it is required.

The researchers compared the efficiency of delivery of a representative drug—the anesthetic and sedative propofol—between three different perfluorocarbons, perfluoropentane (PFP), decafluoropentane (DFP), and perfluorooctylbromide (PFOB). The ultrasound was delivered to the nanodroplets in vitro, in 60 pulses of 100 milliseconds over one minute.

Reaching the boiling point

The results showed that the balance between stability of the nanodroplets and the efficiency of delivery was optimal for PFOB cores.

"Previous studies have focused on perfluorocarbons with low boiling points—usually lower than the human body temperature. We found that droplets with a PFOB core, which has a [boiling point](#) of 142 °C, are much more stable over time," explained Wilson.

"Despite its high boiling point, PFOB can achieve similar levels of drug

release when low-frequency ultrasound of 300 kilohertz is applied. The ultrasound frequency turned out to be a critical factor in our study."

To test for safety, the researchers injected a single long-tailed macaque with six doses of PFOB-based nanodroplets at one-week intervals, and monitored the evolution of a range of blood biomarkers for liver, kidney, and immune response function. This experiment, which had been approved by University of Utah Institutional Animal Care and Use Committee, showed that the nanodroplets were well tolerated, with no detectable side effects. These experiments must be replicated in microdosing or Phase I trials on human volunteers.

The authors also published their protocol for the production of the nanodroplets as open science, so other research groups can learn directly from their findings.

"The method we developed can be applied to any of a variety of conditions depending on the [drug](#) used. For psychiatric applications, localized delivery of propofol could be used as a diagnostic tool to identify brain regions causally involved in disorders for individual patients. For more lasting treatment, ketamine delivery could be a potent method to rewire [neural circuits](#)," concluded Wilson's academic supervisor, Dr. Jan Kubanek, an assistant professor at the University of Utah, and the study's senior author.

More information: Matthew G. Wilson et al, Targeted drug release from stable and safe ultrasound-sensitive nanocarriers, *Frontiers in Molecular Biosciences* (2024). [DOI: 10.3389/fmolb.2024.1408767](https://doi.org/10.3389/fmolb.2024.1408767). www.frontiersin.org/articles/1...lb.2024.1408767/full

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