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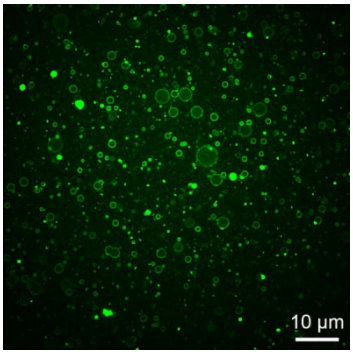
Creating self-assembling capsules for drug delivery

Self-assembling molecules that spontaneously organise themselves to form complex structures are common in nature; for example, the tough outer layer of insects, called the cuticle, is rich in proteins that can self-assemble. Inspired by the cuticles of Asian corn borer moth caterpillars (*Ostrinia furnacalis*), scientists at Nanyang Technological University, Singapore (NTU Singapore) have created nanosized capsules that could be used to deliver drugs and messenger RNA (mRNA), a molecule that instructs cells to produce proteins.

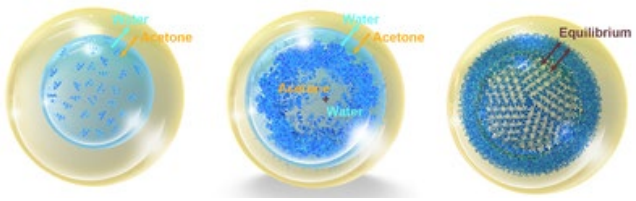


Self-assembly is a cost-effective, environmentally sustainable and quick way of manufacturing nanostructures with critical applications in various industries, ranging from therapeutics to self-replicating machines. The Singaporean scientists analysed the proteins in the cuticle from the heads of Asian corn borer caterpillars to identify chains of amino acids, known as peptides, that could assemble into ordered structures independently.

They screened the proteins for peptides that contained the same sequence of amino acids repeating three or more times, with each sequence consisting of at least five amino acids. Due to the interactions between the repeating amino acids, peptides with this property will likely undergo self-assembly. The scientists identified three peptides that could self-assemble to form hollow nanocapsules from their analysis.

The self-assembly process is driven by differences in chemical concentrations, which cause the peptides to come together like Lego bricks and form stable structures. The scientists created synthetic versions of the natural self-assembling peptides found in the caterpillars and dissolved each peptide in water. They then added the organic solvent acetone to the peptide solutions to initiate self-assembly.

They discovered that self-assembly of the peptides takes place in two stages. First, the peptide solution formed droplets immediately when acetone was added. Next, the diffusion of acetone into the droplets and water out of the droplets creates a concentration gradient at the interface of the droplets that triggers the peptides to assemble into sheet-like structures called beta sheets, eventually forming spherical hollow nanocapsules. The entire process takes place within 10 minutes of the initial mixing.



The concentration gradient at the interface of the droplets, created by the diffusion of water and acetone, drives the formation of nanocapsules. Image credit: NTU Singapore.

The scientists could also fine-tune the nanocapsules' size by adjusting the ratio of peptides to isophorone diisocyanate. This compound links the peptides together to stabilise the nanocapsules. According to Associate Professor Yu Jing, who co-led the study, "this is the first time that peptide nanocapsules have been created without templates, paving the way for a customisable drug delivery system".

The researchers demonstrated that the nanocapsules could be used to trap and deliver 'cargo' such as chemotherapy drugs and antibodies. By modifying the peptide chains, they could also use the nanocapsules to deliver mRNA. The nanocapsules containing drugs and mRNA were not toxic and were successfully taken up by a variety of cells.

"By understanding the behaviour of self-assembling peptides in nature, we can engineer them to deliver a wide variety of drugs and therapeutic compounds," said NTU's Dr Li Haopeng, first author of the study.

With their work now published in the journal *Nature Nanotechnology*, the researchers will next explore using artificial intelligence technologies such as machine learning to identify other natural self-assembling peptides automatically. They are also applying for a patent for their innovation.

Top image: The capsules formed by one of the peptides. Image credit: NTU Singapore.

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