(SD2025-055) A SYNTHETIC BIOMOLECULAR CONDENSATE FOR ON-DEMAND ANTICOAGULATION: This material automatically releases the anticoagulant heparin when thrombin (clotting factor) levels get too high.

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ABSTRACT

Stability issues in membrane-free coacervates have been addressed with coating strategies, but these approaches often compromise the permeability of the coacervate. Researchers from UC San Diego have invented a facile approach to maintain both stability and permeability using tannic acid and then demonstrate the value of this approach in enzyme-triggered drug release. First, the researchers developed size-tunable coacervates via self-assembly of heparin glycosaminoglycan with tyrosine and arginine-based peptides. A thrombin-recognition site within the peptide building block results in heparin release upon thrombin proteolysis. Notably, polyphenols are integrated within the nano-coacervates to improve stability in biofluids. Phenolic crosslinking at the liquid-liquid interface enables nano-coacervates to maintain exceptional structural integrity across various environments. The UCSD scientists discovered a pivotal polyphenol threshold for preserving enzymatic activity alongside enhanced stability. The disassembly rate of the nano-coacervates increases as a function of thrombin activity, thus preventing a coagulation cascade. This polyphenol-based approach not only improves stability but also opens the way for applications in biomedicine, protease sensing, and bio-responsive drug delivery.

TECHNOLOGY DESCRIPTION

Researchers from UC San Diego developed a stable and enzyme-responsive coacervate platform. They first engineered a nano-sized coacervate made of bio-inspired peptides and the anticoagulant heparin. Heparin plays an important role in surgical and cardiovascular

OTHER INFORMATION

KEYWORDS

anticoagulation, thrombosis, heparin

CATEGORIZED AS

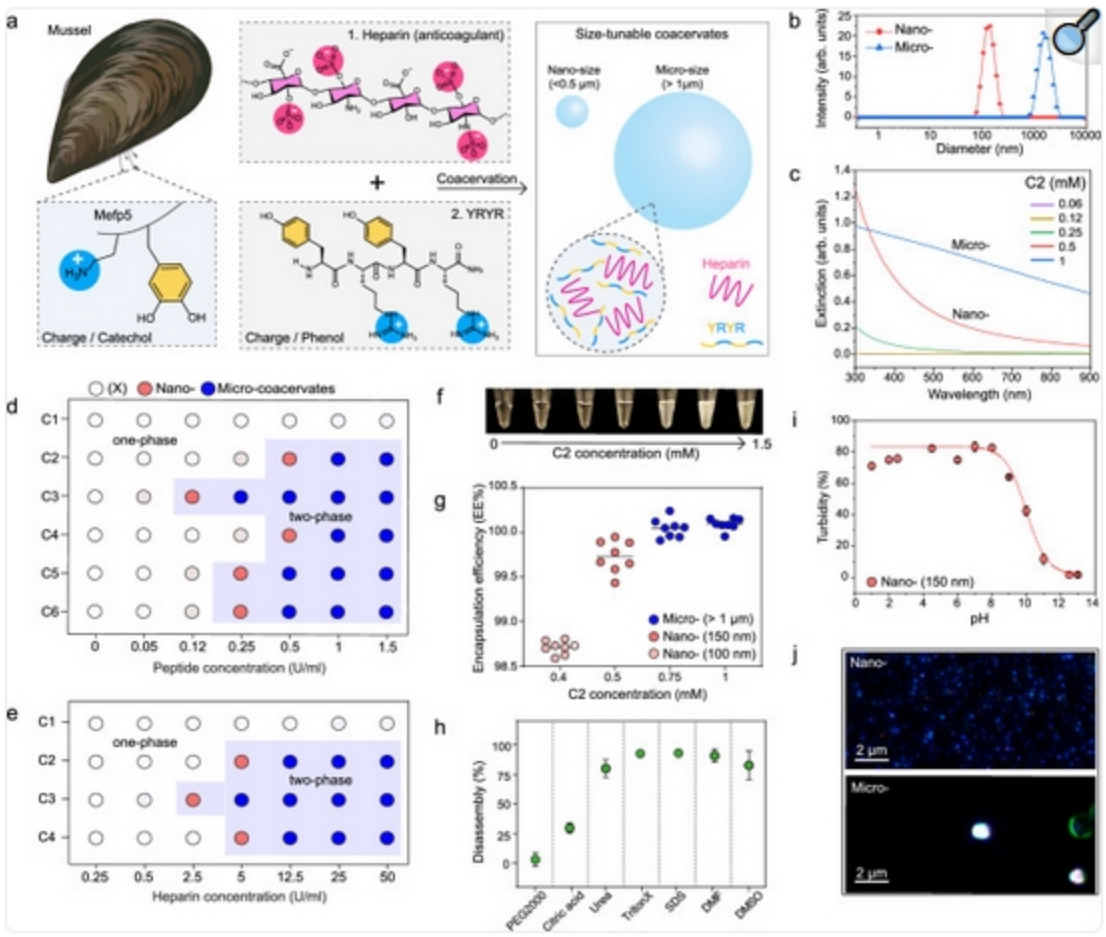
- **Medical**
  - Disease: Cardiovascular and Circulatory System
  - New Chemical Entities, Drug Leads

RELATED CASES

2021-Z08-1

medicine due to its short half-life, reversible nature, and low cost. However, heparin is difficult to manage and requires blood draws and central labs, therefore, the controlled release of heparin via the enzymatic activity of clotting factors is gaining interest. Living organisms maintain hemostasis through precise molecular feedback regulations. For example, vascular injury triggers a coagulation cascade process where clotting factors activate prothrombin to thrombin, transforming fibrinogen into insoluble fibrin by cleavage. Together with platelet activation, this process produces stable fibrin clots to prevent excessive bleeding. The inventors envision that by incorporating a feedback loop system within the coacervates, they could regulate heparin release based on thrombin activity. Increasing environmental thrombin levels would promptly trigger heparin release, while normal physiological thrombin levels would leave the coacervates intact—thus, there would be no risk of excessive bleeding.

Fig. 1. Size-tunable coacervate driven by YR-heparin interactions.



a Schematic illustration of coacervate design using heparin and a YR-based short peptide. **b** DLS data of C2-heparin coacervates, showing their nano (198 ± 3.3 nm) or micro (>1 μm) sizes. **c** UV-vis spectra of nano- and micro-coacervates. Formation of coacervates as a function of different peptide (**d**) and heparin (**e**) concentrations. Six different peptide sequences (details described in Table 1) are examined to study the impact of the charge, concentration, number, thrombin recognition site, and length of YR-based peptides for heparin coacervation. The blue area indicates coacervate formation (i.e., phase separation). Red and blue dots indicate nano- and micro-sized coacervate formation, while empty dots represent no coacervate formation. **f** The photograph shows the increased turbidity as a function of coacervate formation. **g** High encapsulation efficiency of nano- and micro-coacervates. Eight dots indicate the encapsulation efficiency of eight independent coacervate samples. Stability test of nano-coacervates in different conditions (**h**) including PEG2000, citric acid, urea, Triton X-100, SDS, DMF, and DMSO, and different pH (**i**). **j** M-NTA images of nano- and micro-coacervates. Small blue dots represent monodispersed nano-coacervates, and large white dots indicate scattered micro-coacervates. The experiment was repeated three times independently with similar results. Data in (**h**) and (**i**) represent mean ± SD (n = 3). Figure 1/panel (**a**) Created with BioRender.com released under a Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International license.

APPLICATIONS

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ADVANTAGES

STATE OF DEVELOPMENT

INTELLECTUAL PROPERTY INFO

UC San Diego has international patent rights (patent-pending) available for commercial development.

RELATED MATERIALS

▶ Yim W, Jin Z, Chang YC, Brambila C, Creyer MN, Ling C, He T, Li Y, Retout M, Penny WF, Zhou J, Jokerst JV. Polyphenol-stabilized coacervates for enzyme-triggered drug delivery. Nat Commun. 2024 Aug 24;15(1):7295. - 08/24/2024

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