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Preview

Multiphase Drug Release in Hollow Multishelled Structures

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Recently in *Nature Communications*, Profs. Dan Wang, Suojiang Zhang, and colleagues report a highly versatile drug-delivery platform showing a promising step toward a sequential-release capability. In careful detail, they report drug-release profiles, mass-transport phenomena, and applications for enhanced bacterial sterilization.

Multifunctional nanomaterials have been widely used to deliver therapeutics to sites of infection or injury. Compared with non-specific systemic drug delivery, which can globally induce adverse side effects, nanomaterials can provide localized and versatile release of therapeutic molecules of interest.[1] In particular, several nanomaterials (i.e., nanoparticles) have been utilized for enhancing capabilities in the design of advanced drug-delivery platforms. Incorporation of physiochemical properties and stimulus-responsive moieties within nanomaterials allows researchers to control local drug concentrations in a spatially and temporally controlled manner.[2] Physical moieties can include polymeric or structural barriers[3] to prevent drug diffusion and slow kinetic release, whereas chemical components can consist of bonding interactions (i.e., covalent, non-covalent [π-π interactions], or hydrogen bonding) between therapeutic molecules and the delivery vehicle.[4] Internal and external stimulus-responsive properties involve the release of drugs under a stimulus such as pH, light, or a foreign substance.[2] All three moieties can work in tandem to provide maximum control over drug delivery.

Still, incorporating each aspect into a single nanoplatform has several challenges. First, drug-loaded nanomaterials often experience an initial burst release of drug molecules. Although this can be beneficial in the short term (i.e., 0–24 h), sites of injury or bacterial infection can require an additional sustained release of drugs.[5] To this end, researchers have focused on developing drug-delivery platforms capable of burst release, sustained release, and stimulus-responsive release of therapeutic molecules (Figure 1A). Previous reports include polymeric materials (such as poly(lactic-co-glycolic acid) nanoparticles for the delivery of antibiotics,[6] inorganic materials such as gold nanoclusters for drug delivery,[7] and mesoporous silica cages for stimulus-responsive drug delivery.[8] But the incorporation of all three functions simultaneously remains a critical challenge. Of particular interest are hollow micro- and nanoparticles, which consist of an inner empty cavity capable of high-capacity drug loading. These bioinspired, hollow nanomaterials have been reported to have tunable mass-transport properties, composition, and design, thereby conferring potential advantages in the design of a multifunctional drug-delivery vehicle.[9] Nonetheless, the design of sequential drug delivery and the detailed examination of mass transport of drug payloads experiencing different drug-release barriers have yet to be fully elucidated. Thus, because drug delivery for conditions such as bacterial infection requires multiphase drug release, hollow multishelled structures could yield superior outcomes.

Recently in *Nature Communications*, Wang, Zhang, and colleagues from the Chinese Academy of Sciences report a hollow multishelled structure (HoMS) with promising initial burst, sustained, and stimulus-responsive drug-release properties and characterize its detailed mass-transport phenomena.[10] First, the authors synthesized a titanium dioxide (TiO_2) HoMS particle (TiO_2-HoMS) by using a sequential templating approach, which allowed the team to demonstrate the ability to synthesize TiO_2-HoMS with two or three individual shell layers, mimicking a concentric particle design (Figure 1B). Furthermore, given that multishelled particles are frequently used tools for drug delivery, the authors chose to address possible antibacterial applications by studying the drug-release kinetics and mass transport of antibacterial agents. For this purpose, Wang and co-workers loaded methylisothiazolinone (MIT), a common antibacterial agent, into TiO_2-HoMS (MIT-TiO_2-HoMS). Characterization of the drug-loaded TiO_2-HoMS revealed a redshift in the C=O range during MIT loading in TiO_2-HoMS, which implies varying drug-adsorption modes according to the authors. They surmised that bonding interaction through S and TiO_2 weakened the C–S bonds present in MIT. Furthermore, their energy-dispersive X-ray spectroscopy mapping of MIT-TiO2-HoMS exhibited homogeneous distribution of MIT drug loading, implying that the shell (outer layer) of TiO_2-HoMS is homogeneous during

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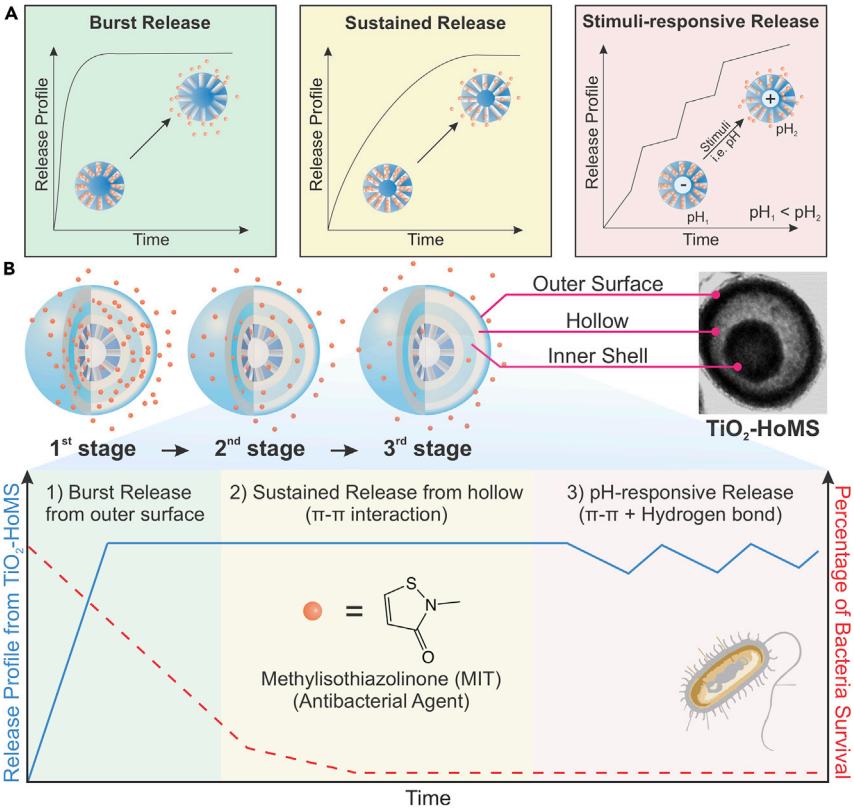

Figure 1. Hollow Multishelled TiO_2-HoMS for Multiphase Release of Antibacterial Agents

(A) Profiles of different drug-release mechanisms: burst release, sustained release, and stimulus-responsive release.

(B) Stages of drug release from different compartments of TiO_2-HoMS particles (the transmission electron microscopy [TEM] image shows the structure of 3s-TiO_2-HoMS). The first stage, driven by concentration gradient, is burst release from the outer surface of the HoMS. The second stage, driven by the balance between concentration gradient and π-π interaction between MIT molecules, is sustained release from the hollow between each shell. The third stage is pH-responsive release upon increased acidity (decreased pH). The TEM image is adapted with permission from Wang and co-workers,[10] copyright © 2020 Springer Nature.

synthesis, an obstacle for the field of multishelled-particle synthesis.

Wang, Zhang, and co-workers carefully investigated the thermal release of MIT from MIT-TiO_2-HoMS through thermal gravimetric analysis (TGA) and differential thermal analysis (DTA) to probe each stage of release. Specifically, they report a sequential release through potential first, second, and third stages (Figure 1B). This pattern was observed for both double-shell TiO_2-HoMS (2s-TiO_2-HoMS) and triple-shell TiO_2-HoMS (3s-TiO_2-HoMS). Importantly, the possible sequential release was due to the unique properties of HoMS. The authors attribute the first stage of release to the evaporation of water in TGA and DTA, whereas concentration gradients and a lack of a physical barrier induce burst drug release in solution. Importantly, burst release is a valuable nanomaterial-based phenomenon that can be essential for treating acute infection or disease. Nonetheless, an obstacle of drug delivery is to maintain a local minimum efficacious concentration, especially concerning bacterial infection. To this end, the authors note that the potential second-stage (sustained) release was attributed to MIT release from the outer shell and the area between individual shells, where MIT molecules interact via π-π stacking. The third stage monitored through DTA and TGA was reportedly due to MIT hydrogen bonding to individual shells. Excitingly, HoMS structures with increasing shell numbers showed excellent drug-loading capacity, demonstrating potential for a more effective and sustained delivery platform of therapeutics. With regard to mass-transport analysis, the investigators determined that MIT adsorption underwent a "multimolecular" adsorption under the Freundlich model.

Next, the team investigated local concentrations and attenuation of bacterial growth in the presence of MIT-TiO_2-HoMS. Bacterial growth and infection are common occurrences in food poisoning, tuberculosis, pneumonia, and many more. Mitigating bacterial growth for long periods is necessary for completely preventing re-infection. To this end, Wang, Zhang, and their team analyzed the first and second stages of MIT release and demonstrated the potential for burst-release kinetics with MIT-loaded particles (first stage) and sustained local concentrations (second stage). Excitingly, they also found that treatment of 3s-MIT-TiO_2 HoMS mitigated bacterial growth in lysogeny broth for over 400 h, approximately ten times longer than that of free MIT drug. After these promising results, the authors analyzed the stimulus-responsive release properties of TiO_2-HoMS. In this regard, the team allowed each experimental condition (i.e., MIT, hollow TiO_2, 2s-MIT-TiO_2-HoMS, 3s-MIT-TiO_2-HoMS, and SBA-15) to reach equilibrium. Interestingly, the team observed an initial decrease in MIT concentration after the addition of bacteria and then, shortly afterward, an increase in MIT concentration to return to equilibrium. This phenomenon indicates a promising first step toward a stimulus-responsive drug-delivery system involving the sequential addition of

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bacteria over a period of several hundred hours. Lastly, Wang, Zhang, and co-workers demonstrated that their TiO_2-HoMS material is pH responsive, whereby increased acidity accelerates MIT release.

Overall, the team has reported a multiphase drug-delivery vehicle with promising properties of temporal release (i.e., burst release, sustained release, and stimulus-responsive release). Furthermore, the complexity of TiO_2-HoMS with multiple shells and a hollow core has conferred several different types of interactions between drug payloads and delivery vehicles. MIT-loaded TiO_2-HoMS interacted with each structural component of TiO_2-HoMS, including the outer surface, inter-shell cavities through π-π interactions, and hollow core through hydrogen bonding. The authors reported that increasing the number of shells on the HoMS increases the drug loading through capillary force and thus results in superior drug loading and sustained drug release. As an antibacterial agent, 3s-MIT-TiO_2-HoMS demonstrated enhanced bacterial death even after additional bacteria were added several times. This achievement improves research on HoMS-mediated drug delivery and offers new insights into drug-release kinetics and mass transport. And, although the reported demonstration targets bacterial growth, drug delivery through TiO_2-HoMS materials could be further applied to a broad range of medical applications requiring a sustained, localized delivery platform.

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