Hollow Micro-/Nanostructures: Improved Materials for Applications in Biomedicine

Kim Ta Literature Seminar September 29, 2016

Research in chemotherapeutic drugs delivery is an important aspect of biomedical development and applications. Many anticancer drugs such as doxorubicin (DOX) are effective in treatment; however, these chemotherapeutic drugs are harmful and toxic to healthy tissues and organs such as heart, bone marrow, liver, and kidney.[1,2] Therefore, the growing demands for developing new drug delivery materials aimed at improving safety and drug delivery efficiency are driving research efforts. An interesting class of new drug delivery vehicles utilize a hollow micro-/nanostructure (ranges from hundreds of nanometers to a few microns) in which the cavity is loaded with desirable drugs while the outside shell protects the cargo from unwanted interactions and uptake by body proteins or phagocytes.[3] Hollow and micro-/nanostructures have many advantageous properties such as exceptionally high surface areas, greater pore volumes compared to regular nanostructures, and tunable pore sizes.[4,5] In addition to their use as drug delivery carriers, these structures can also be used as imaging agents in photothermal therapy when stimulated by near infrared radiation.[4]

The procedures for creating hollow structures for application in drug delivery are complex. The hollow and micro-/nanostructures must have uniform morphology to enable reproducible properties and facilitate scalability.[4] Research in this field has improved significantly over the years, culminating in mature techniques to synthesizing different types of materials. Figure 1 outlines various synthetic methods used to make hollow nanostructures.[5] A variety of synthesis techniques are employed including:

(1) hard-templating methods (Fig. 1a) in which the template is prepared, coated with the shell material, and subsequently removed

(2) soft-templating methods (Fig. 1b) usually involving the coating process with no need to prepare a hard, inner template

(3) multiple-templating methods (Fig. 1c) in which both hard- and soft-templating procedures are utilized

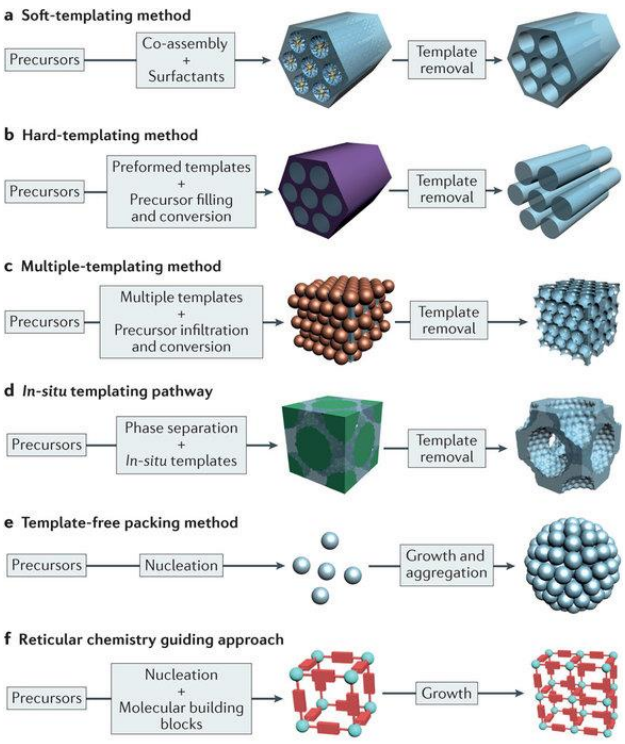

Figure 1. Common synthetic methods to prepare hollow micro-/nanostructures.

(4) *in-situ* templating (Fig. 1d), in which either precursors or solvents can become a template from simple phase separation
(5) a template-free packing method (Fig. 1e), where the structure is grown from coagulated nanometer-sized precursors
(6) reticular chemistry guiding approach (Fig. 1f) is the most unique synthetic technique, which forms large organic frameworks from their molecular components.[4,5]

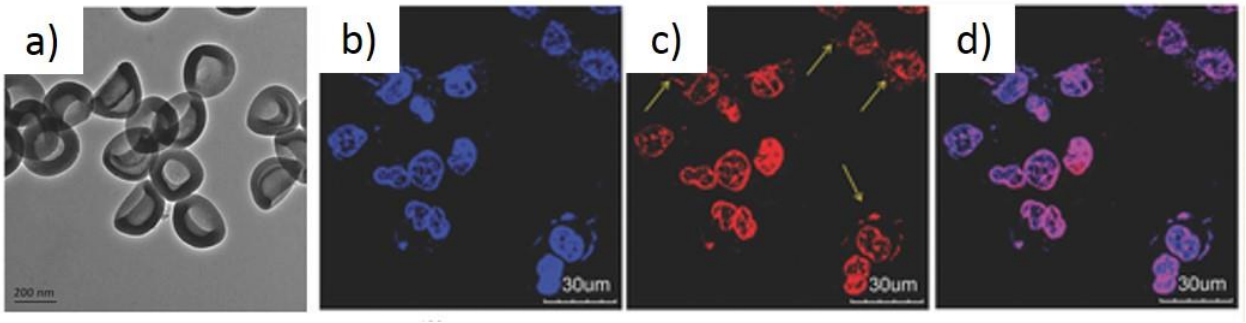

Figure 2. a) TEM images of hollow nanocapsules with clear contrast between the shell and the empty cavity. b-d) CLSM images show that DOX molecules encapsulated in hollow nanostructures successfully enter cancer cells.[5]

Hollow and micro-/nanostructures have been shown to carry a variety of drugs, including cancer treatment drug such as doxorubicin (DOX)[1,3,6,7] and ibuprofen.[8,9] Due to their empty cavity and carbonaceous shell, the hollow nanocapsules have higher drug loading ability compared to solid nanoparticles as well as favorable interaction with aromatic drug molecules. Additionally, the morphology of the hollow nanospheres is similar to that of a red-blood cell (RBC) assisting in the hollow nanocapsule's ability to distort and squeeze into narrow pathways, improving delivery efficiency compared to regular nanostructures (Fig. 2a). Furthermore, the clear contrast between the thicker shell and the hollow center can be easily distinguished under the electron microscope. Fig. 2b-d depict confocal laser scanning microscopy (CLSM) images of the blue-dyed nuclei, red-dyed DOX-loaded hollow nanocapsules, and merged images showing DOX molecules are delivered into cancer cells after co-incubation.[6]

Since hollow and micro-/nanostructures can be loaded with both imaging agents and drug molecules simultaneously, image-guided therapy has been attracting a lot of research and development.[1,2,10–14] Hu and coworkers synthesize and test double-walled Au nanocage/SiO_2 nanorattles as DOX delivery vehicle and photothermal therapeutic imaging materials. As seen in Fig. 3a-d, the Ag nanocubes are first converted to hollow Au nanocages then encapsulated by a thin and porous silica shell, creating Au/SiO_2 nanorattles. *p*-aminothiophenol (*p*ATP) molecules are capped onto these nanorattles, which helps to enhance sensitive SERS signals for monitoring cells, while DOX is loaded onto the porous silica shell. Furthermore, the Au/SiO_2 nanorattles can be stimulated by near infrared radiation producing heat to use in photothermal therapy. The combination of anticancer drug delivery and photothermal therapy capabilities results in cancer cells death with the lowest cell viability percentage across concentrations (cyan bars in Fig. 3e).

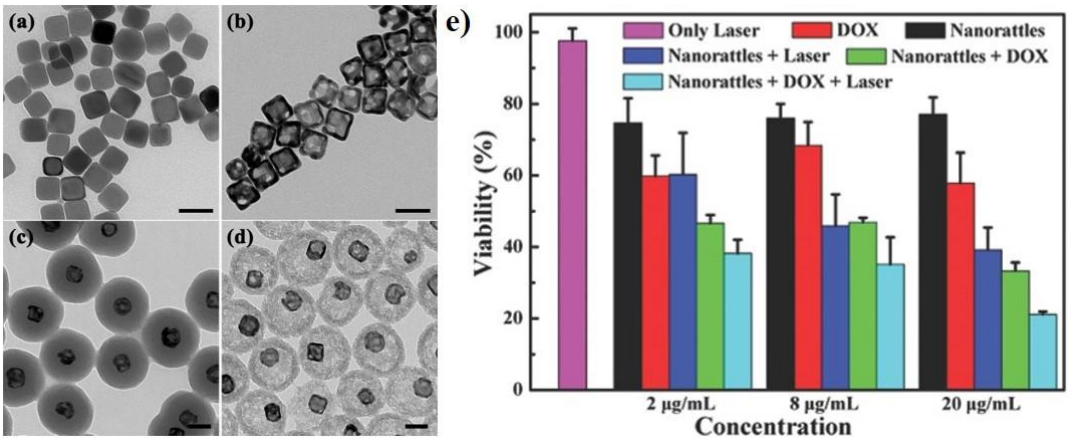

Figure 3. a-d) TEM images of Ag nanocubes successfully converted to hollow Au nanocages encapsulated by a porous SiO_2 layer. e) Cancer cell viability decreases when DOX is delivered using the nanorattles with laser assist treatment.[13]

Many challenges must be overcome such as scalability, production cost, and human compatibility before hollow and micro-/nanostructures can be used as drug delivery agents. Most of these structures are made in the laboratories in small scale settings, but industrial applications require hundreds of kilograms of materials, which will also raise production cost. Careful research is required to study compatibility and toxicity of micro-/nanostructures in the human body. In future research, it is important to address and overcome the aforementioned issues before hollow and micro-/nanomaterials can be widely used. Nonetheless, the field has attracted significant attention from researchers in the past decade, increasing the number of suitable compounds and materials as well as their potential applications in biomedicine.

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