Polymer Carriers

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Triggering Release of Encapsulated Cargo**

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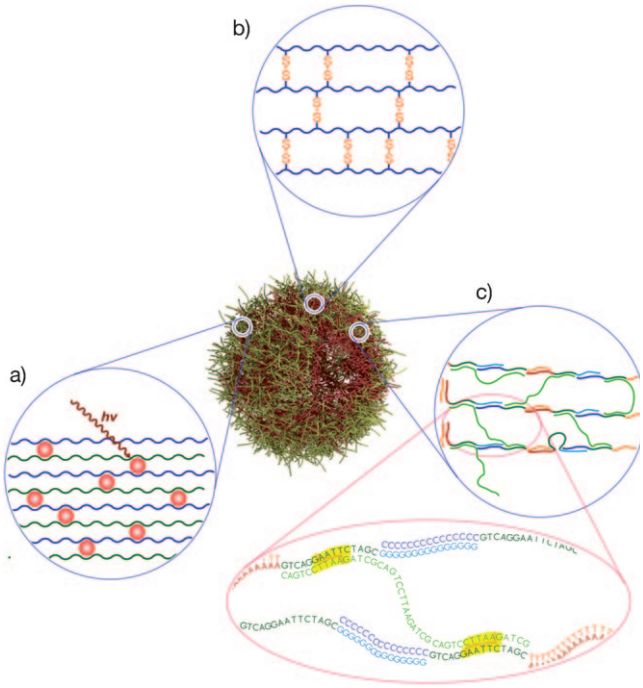
The encapsulation of materials within polymer carriers is important for developments in drug delivery, biosensing, catalysis, and microreactors. Polymer carriers can be synthesized using a variety of techniques, including self-assembly (e.g., polymer micelles[1a] and polymersomes[1b]) and templated assembly (e.g., layer-by-layer (LbL) capsules,[2a,b] polymerized emulsion droplets,[2c] and nanoimprint lithography particles[2d]). Of equal importance to developing effective encapsulation techniques is the ability to control the release of the encapsulated contents. Triggering the release of such encapsulants can be achieved through a number of different mechanisms, which can be broadly separated into two types: one where an external stimulus is applied, and the other, where a change in the local (e.g., chemical) environment induces a change in the carrier permeability and thus release of the encapsulated cargo. Engineering mechanisms into the carriers to control cargo release is an area of active research and has recently led to a number of important advances in the area.

A distinct advantage of using an external stimulus is that cargo release from capsules can be controlled remotely and on demand. Near-infrared (NIR) radiation has been used extensively as an external release trigger because this stimulus can be applied in a focused area, allowing localized release from individual capsules (Scheme 1 a). The use of NIR light is particularly relevant for biomedicial applications, as tissue absorption is negligible in the region between 800 and 1200 nm.[3] A number of materials with tunable absorption characteristics (e.g., gold and silver) can effectively absorb NIR light, leading to significant localized heating. NIR irradiation of LbL polymer capsules that contain gold nanoparticles[4] causes localized heating (> 600 °C[4a]) and destruction of the capsules, but it does not significantly affect the capsule cargo or surrounding cells. This approach has been used to release encapsulated peptides, proteins, and model drugs. Release can be achieved over a large area (> 1 cm^2),[4a,b] using a diffuse laser beam, or localized on an individual capsule inside a cell.[4c] On a smaller scale, polymer-coated gold nanocages have also been demonstrated to undergo NIR-light-triggered release.[4d] By using the temperature-responsive polymer, poly(*N*-isopropylacrylamide) (PNIPAm) release occurs as a result of a change in the polymer conformation upon heating. Carbon nanotubes (CNTs) are another class of material that are capable of absorbing light in the NIR spectrum. Fréchet and co-workers recently demonstrated that CNTs can be encapsulated in a microcapsule by cross-linking an emulsion droplet in situ.[2c] These liquid-filled polymer capsules were coloaded with a range of small molecules, such as reaction substrates or gelation catalysts. When irradiated with NIR light, the capsules ruptured, and release was monitored by reaction of these species with other small molecules in solution. Similar to the NIR-light studies, UV irradiation has also been used to release encapsulated materials from polymer microcapsules containing nanoparticles (TiO_2).[5] This approach is likely to be focused at applications in cosmetics and agriculture.

The release of capsule cargo through an inherent biological stimulus is of immense interest for therapeutic applica-



Scheme 1. Examples of triggers to release encapsulants from polymer carriers: a) light (NIR-light-absorbing nanoparticles), b) redox potential (cleavage of disulfide bonds), and c) enzymes (enzymatic cleavage).

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tions. Commonly exploited environmental triggers that have been used to induce release in polymer carriers include changes in the environmental pH and temperature. This work has been the subject of a number of comprehensive reviews.[6] However, there has been a number of significant advances in the field of triggered release using other intrinsic stimuli,[7] including changes in redox potential (thiol–disulfide exchange; Scheme 1b),[8,9] enzymatic degradation (Scheme 1c),[10,11] and degradation in response to the presence of a specific metabolite.[12]

Release of encapsulated cargo can be desirable outside the cell. This is important for the treatment of diseases such as diabetes, where the delivery of insulin required is based on the concentration of glucose in the bloodstream.[12] LbL capsules containing glucose oxidase and catalase have been designed with tunable permeability; the capsules respond to the presence of glucose, thus providing an ideal trigger for the release of insulin.[12a] The increase in permeability is caused by a decrease in pH as a result of conversion of glucose into gluconic acid and hydrogen peroxide, catalyzed by glucose oxidase. A glucose-responsive system has also been developed based on glucose oxidase encapsulated in oxidatively responsive polymersomes.[12b] In the presence of glucose, the polymerosomes are destabilized owing to the formation of hydrogen peroxide by the glucose oxidase/glucose/oxygen system.

In drug delivery, it is often desirable for drug release when the capsules are internalized by cells. This can be achieved by exploiting the change in the redox potential between the extracellular and intracellular environments. Thiol–disulfide exchange can be exploited to induce capsule degradation (and hence cargo release), as disulfide bonds within the capsules are stable in the oxidizing environment outside the cell, but are cleaved in the reducing environment of the cell. Disulfide bonds have been used to stabilize a variety of polymeric capsules, including cross-linked micelles,[8a–c] polymersomes[8d] and LbL capsules,[9] and to release cargo such as nucleic acids, peptides, and anticancer drugs. For example, micelles with disulfide-stabilized cores can degrade upon cell internalization.[8a,b] Poly(ethylene glycol) (PEG)/poly(aspartamide) micelles, with cell-cleavable PEG chains, have also been shown to facilitate the delivery of plasmid DNA.[8c] Thiol-modified poly(methacrylic acid) LbL capsules have been shown to exhibit tailored degradation properties under simulated cytoplasmic conditions,[9c] and can release immunogenicly active cargo both in vitro[9d] and in vivo.[9e]

Polymer carriers can also be engineered to degrade in the presence of an enzyme.[10,11] This can be achieved by assembling the carriers with polymers that are inherently degradable. Capsules synthesized from naturally occurring polymers, such as polypeptides or sugars, are susceptible to nonspecific degradation as a result of ubiquitous peptidases and carbohydrases.[10] However, capsules can also be engineered to degrade specifically in the presence of certain enzymes that have more specific substrates.[11] LbL-assembled DNA capsules have been shown to degrade in the presence of a restriction enzyme that recognizes only a specific sequence of DNA.[11a] Polymer carriers synthesized using nanoimprint lithography have been formed by cross-linking modified PEG with a peptide sequence that is specifically degraded by the lysosomal enzyme cathepsin. Upon exposure to cathepsin, proteins and plasmids were released from the particles.[11b]

The examples highlighted demonstrate some of the recent advances in the field of triggerable release of encapsulants from polymer carriers. To date, most studies have focused on the design and proof-of-principle application of the trigger mechanisms. One of the principal challenges in this field is to ensure that the rate of release can be controlled so it will occur in a time frame that is biologically relevant. In the coming years we anticipate that further development of trigger-responsive carrier systems will significantly extend their application to in vivo systems for therapeutic applications, as well as advanced catalysis and microscale reactions.

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