Drug Delivery

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pH-Responsive Micro- and Nanocarrier Systems**

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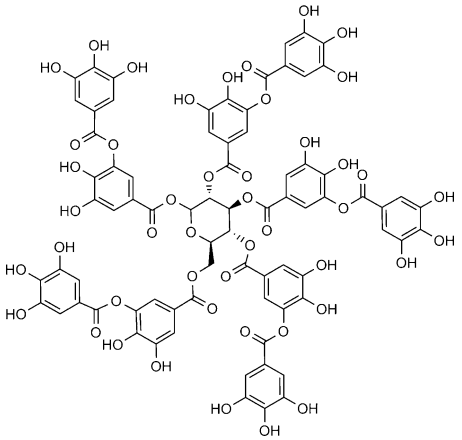
One of the major challenges in drug delivery is the targeted release of a cargo which can be triggered by a stimulus. A release stimulus that is often used is the pH gradient between the extra- and intracellular regions and between healthy and diseased tissue.[1] Thus, a pH-sensitive transporter can selectively deliver its cargo into cells by endocytosis or into inflamed tissue.

Biocompatible transport systems are especially interesting for the encapsulation and release of sensitive biological payloads under mild conditions. The transport system should improve the limited bioavailability, solubility, biodistribution, and duration of blood circulation of the cargo.[2] Another important factor is the biodegradability or blood clearance of the carrier after transport and delivery of the cargo. Micro- and nanocarriers based on macromolecular architectures and stable self-assemblies can be tailor-made to meet all these requirements. pH-Responsive bonds allow the degradation of the carrier and the targeted release of the payload at low pH.

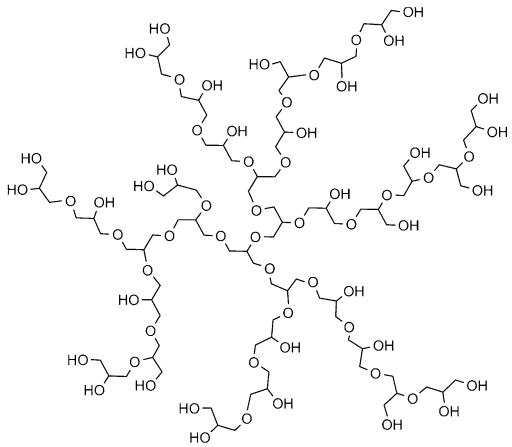
In this Highlight we focus on novel biocompatible micro- and nanotransport systems that are able to encapsulate biological matter without damaging the payload during entrapment and can be triggered by a slightly acidic pH to release the load. We compare different approaches for the encapsulation of drugs, proteins, and bacteria with different pH-cleavable moieties that have been recently reported.

Caruso et al. have described a novel micro-encapsulation system for various substrates based on a one-step assembly of coordination complexes between metal ions and tannins, which are naturally occurring polyphenols in plants.[3] Tannic acid (TA) is based on polyphenols coupled to glucose through ester bonds (Scheme 1). Due to these ester linkages, the molecule is biodegradable and its high number of hydroxy groups makes it highly water soluble. The spontaneous complexation of Fe^{III} ions with the TA catecholic unit and the adhesion of TA on diverse surfaces were utilized in a simple approach to form films on a multiplicity of substrates, for example organic and inorganic templates, and even bacteria.

The self-assembly of TA is a pH-dependent process (Scheme 2). At pH < 7 the metal ion forms mono- and bis-complexes with TA, while at pH > 7 one metal ion coordinates to three TA molecules and forms stable films regardless of the size and shape of the template. Due to these properties, the assemblies are stable at physiological pH and disassemble under mild acidic conditions, thereby releasing encapsulated



tannic acid (TA)



dendritic polyglycerol (dPG)

Scheme 1. Comparison of the structures of tannic acid (left) and dendritic polyglycerol (right) as building blocks for micro- and nanotransporters.

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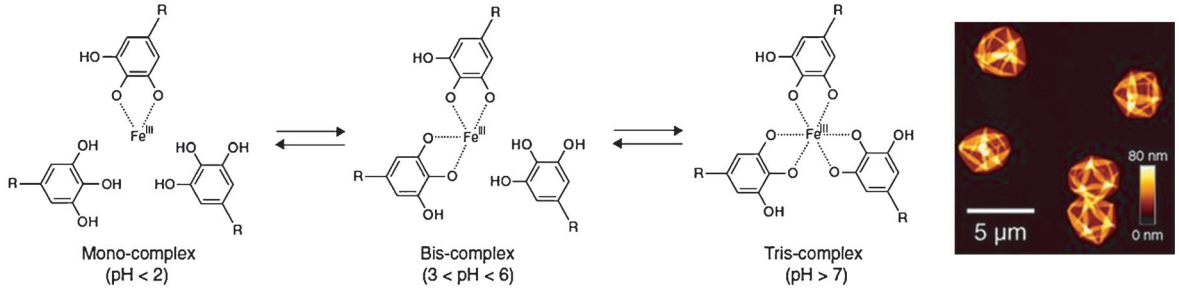


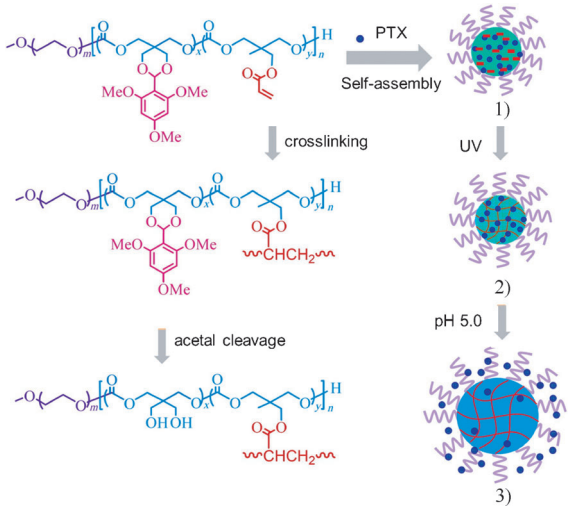
Scheme 2. pH-Dependent coordination of catecholic moieties to iron(III) (left) to form films and capsules (right) on different substrates, for example, polystyrene. Reprinted with permission from Ref. [3].

guests. This makes them interesting candidates for biomedical applications. The possibility of using different metal ions and polyphenols makes this approach highly versatile. The high biocompatibility and low costs of the materials are further crucial benefits for the encapsulation and release of other important payloads such as drugs.

The transport of drugs, especially anti-tumor drugs, is critical since the entrapped cargo must be harmless during transport and regain its cytotoxic activity after liberation in the targeted tissue. For this purpose, nanocarriers must fulfill the above-mentioned criteria and target tumor tissue based on enhanced permeation and retention (EPR).[4] Recent examples for nanometer-sized carriers that fulfill these criteria are the core-crosslinked polymeric micelles described by Zhong et al.[5] These micelles consist of biodegradable diblock copolymers containing acid-labile acetal and photo-crosslinkable acryloyl groups in the hydrophobic polycarbonate block and could encapsulate paclitaxel (PTX) with high loading efficiencies of up to 15 wt%. After crosslinking of the core, the PTX-loaded nanocarriers were stable at physiological pH and the release of the drug was inhibited. At a mild acidic pH of 5, however, the acetal groups were hydrolyzed and PTX was released from the now polar interior (Scheme 3). Empty micelles showed negligible cytotoxicity in a control experiment, while PTX-loaded nanocarriers retained high anti-tumor activities which proved the efficient drug release into tumor cells. However, the cytotoxicity of the encapsulated drug was lower than that of free PTX, since the cellular uptake was slower and the acetal hydrolysis had to be activated in the endosomal compartment. A drawback of this system is the limited degradability of the polyacrylate core after crosslinking.

Degradation of acid-labile acetals is one of the benefits of the bioinert nanogels recently described by Steinhilber et al.[6] Nanogels with tunable sizes between 100 and 1000 nm were prepared by the crosslinking of dendritic polyglycerol (dPG) building blocks by Cu-mediated click chemistry.

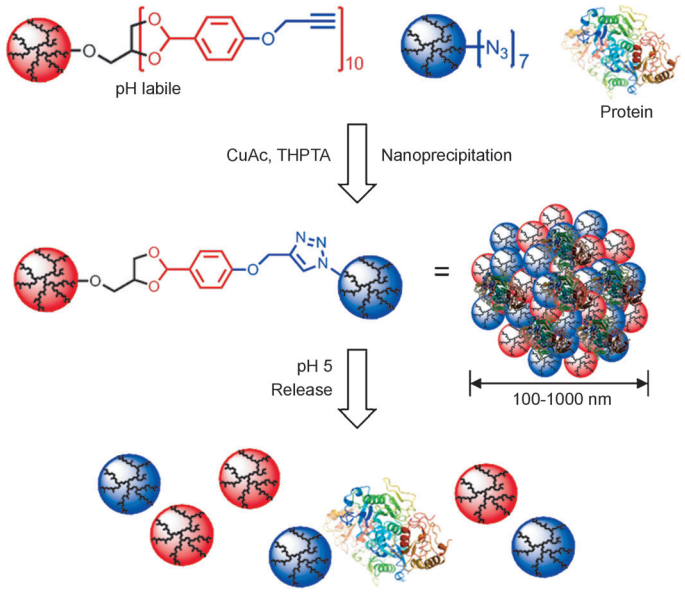
The similarity between dPG and TA is obvious when their structures are compared (Scheme 1). Numerous hydroxy groups and a highly branched polymeric scaffold offer good water solubility and high biocompatibility. In contrast to polyphenols, i.e. TA, the dPG scaffold is highly protein resistant.[7]



Scheme 3. Photo-crosslinkable pH-responsive degradable block copolymer micelles. PTX-laden micelles (1) were crosslinked by UV irradiation (2). Crosslinked PTX-laden nanoparticles showed extracellular stability and release of the drug under mild acidic conditions (3). Reprinted with permission from Ref. [5].

Although unspecific protein interaction is prevented with dPG, the enzyme asparaginase could be encapsulated by dPG nanogels under mild conditions. dPG nanogels were synthesized by surfactant-free and inverse nanoprecipitation. Acid-labile, cyclic benzacetal bonds permit the degradation of the nanogel into small fragments in a mild acidic environment (pH 5). This allows the release of the protein in a cell compartment with mild acidic pH without loss of activity (Scheme 4). Recently, this concept was transferred to a Cu-free click reaction for the encapsulation of living cells.[6]

Although nano- and micrometer-scaled carrier systems for biomedical applications have many advantages, not only biological matter and drugs must be transported and released. In some neurodegenerative diseases, there are metal ion imbalances like the Cu deficiency in Alzheimer's disease.[8] The transport of metal ions and their controlled pH-triggered intracellular release is therefore an important challenge, whereby only a few examples have been reported so far.[9,10] Since the metal-ion release is also a feature of the above-mentioned TA–metal ion complex,[3] this universal carrier



Scheme 4. Protein encapsulation by nanoprecipitation by bioorthogonal crosslinking of dendritic polyglycerols and a pH-dependent degradation of the dPG nanogel with release of the protein.[6]

system has great potential for different kinds of transport applications.

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