

# Nanoscale Horizons

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## MINIREVIEW

### Redefining the functions of nanocapsules materials

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Nanocapsules are key components in new technologies related to biomedicine and materials science. However, their long-term fate after use is still largely ignored. We discuss here a sustainable approach where the products of degradation of the nanoparticles play a significant role for the application because they are also functional molecules. The polymer shell of the nanocapsules is chemically engineered so that the degradation products occurring upon chemical damage are useful after normal service of the nanocapsules.

#### Introduction

Nanocapsules are used as dispersions or embedded in matrices for biomedical and materials applications. However, the long-term fate of the nanoparticles after their use is still largely ignored. Moreover, most of the materials in nanoparticles and nanocapsules are actually “dead materials” in the sense that their degradation product does not play an important function. These materials are either inert or even detrimental to the application if their degradation products are toxic or lower the properties of the matrix in which they are embedded. One possibility to overcome this issue would be to recycle nanoparticles that do not degrade easily. Approaches such as recovery of metallic nanoparticles by inducing a liquid-liquid phase separation by heating microemulsions,<sup>1</sup> decantation of inorganic nanoparticles used as catalysts and as Pickering stabilizers,<sup>2</sup> or filtering nanoparticles with a supramolecular membrane.<sup>3</sup> However, polymer nanoparticles are difficult to be re-dispersed and kept intact. Moreover, recycling nanoparticles is not a concern for biomedical applications.

We discuss here a sustainable approach where the products of degradation of the nanoparticles play a predominant role because they are also functional molecules. This approach considers the lifetime of the nanoparticles. Therefore the nanoparticles have to be carefully designed, keeping in mind that the material composing the nanoparticles is used to yield functional degradation products. The approach can be combined with retrosynthetic analysis<sup>4</sup> with additional conditions concerning the degradation products. Similarly to the renewable carbon index (RCI) for green chemistry, we define here the active molecule index (AMI). The AMI is the percentage of active molecules within all degradation products of the nanoparticles. We review briefly here the different strategies to

synthesize nanocontainers that release functional molecules upon their degradation and discuss their AMI values. We envision a future of colloid chemistry for which the Latin adage “*multum in parvo*” (much in little) will be truly applied by designing efficient nanocontainers that will serve not only during but also after their life time.

#### From classical synthesis to the design of sustainable nanocontainers

Classically, the synthetic molecules around us produced by the industry are designed following retrosynthetic analysis with requirements about cost and availability of the raw chemicals. Because of the new concerns of the society regarding sustainability, several principles of synthesis were introduced as green chemistry label.<sup>5,6</sup> One important value linked with sustainable chemistry is the so-called renewable carbon index (RCI). The RCI is the percentage of carbon in the synthesized molecule that originates from a renewable feedstock.<sup>7</sup> Typically, the carbon atoms from renewable feedstocks come from fatty acids or glycerol for example.<sup>8,9</sup> Nowadays, further requirements imply that the renewable feedstock shall not compete with the food chain. This is the case for instance of L-lactide, cellulose, or terpenes. This means that the main concerns are that the raw material is cheap and is derived from renewable resources.

The function of nanocontainers can be typically fulfilled at low concentrations.<sup>10</sup> This means that the concern about cost and renewable feedstock are less important because they do not represent a large fraction of the materials compared to the matrix in which they are embedded. The most important criteria to design the nanocontainers are their functions, the encapsulation efficiency, and their degradation,<sup>11</sup> especially when they are employed for biomedical applications. However, nanotoxicology is an issue and there no consensus yet on the harmonization of experimental procedures to investigate the toxicology of nanoparticles.<sup>12</sup> For biomedical applications, the polymer matrix can be degraded by hydrolysis, oxidations, or enzymatic reactions.<sup>13</sup> The nanoparticles can have however a detrimental effect after their primary function is achieved. It was reported for instance that the

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degradation of nanoparticles of the popular poly(D,L-lactide), poly( $\epsilon$ -caprolactone), and poly(lactide-co-glycolide) displayed high toxicity for all the tested cell lines at high concentration.<sup>14</sup> Usually, the amount of polymer matrix in nanoparticles for biomedicine is much larger than the amount of drugs that are encapsulated in the polymer matrix. Similarly, the polymer shells of microcapsules used for self-healing materials are usually non-useful materials. After delivery of the healing agents, empty microcapsules remain in the matrix and become preferential location for crack propagation or attack from external media. They are thus detrimental to the properties of the materials. We discuss here how the synthetic approach employed to design nanocontainers can be modified to implement a useful function to the nanocontainers even after their normal service.

### Chemical encoding of functional molecules in nanocontainers

A classical method to lower the toxicity of the drug is to fabricate a prodrug that is later metabolized to yield the active form of the drug in the body. Nanocontainers are often used to encapsulate and protect prodrugs. For instance, nanoparticles based on chitosan derivatives were used as nanocarrier for neuropeptides to prevent plasma degradation.<sup>15</sup>

The chemical encoding of active substances in a macromolecular chain was introduced by Ringsdorf for the delivery of drugs<sup>16</sup> (see Fig. 1). The polymer comprised several segments that have different roles: A segment ensuring the solubilization of the polymer, the pharmacophore to be delivered in the body, and one unit for targeted delivery. Many of such polymers do not contain the unit for targeting and are called polymer prodrugs. A now classical method to transport and release drugs is to conjugate them with a polymer.<sup>17,18</sup> Such a strategy can be employed to formulate nanoparticles that are constituted of the polymer-drug conjugate. Several approaches were identified: The conjugation of a drug to a pre-synthesized polymer, the conjugation with a monomer followed by polymerization, and the initiation of a polymerization by a functionalized drug.<sup>19</sup> The anticancer drug cisplatin was conjugated to a diblock copolymer forming micelles *via* hydrazone bonds and the drug could be released to the acidic medium of the tumor cell.<sup>20</sup> The advantage of such an approach is that the drug is protected during its transport to the tumor cells. Gemcitabine, also an anticancer drug, was conjugated to reversible addition-fragmentation chain transfer (RAFT) agents for polymerizing squalenyl methacrylate<sup>21</sup> and methyl methacrylate.<sup>22</sup> The polymers could self-assemble to form nanoparticles in water that allowed for a pH-dependent release of gemcitabine. Similarly, alkoxyamines for nitroxide mediated polymerization (NMP) were functionalized with the same drug to yield nanoparticles.<sup>23</sup>

However, the quantity of drug compared to the polymer is still low. A method to increase the amount of useful active material incorporated, the so-called AMI value, is to use a drug or another active substance as monomer or to graft it as side chain of the polymer with a high grafting ratio.

Fig. 1

The concept is particularly simple to achieve when polymers are synthesized by polyaddition or polycondensation reaction because the active molecules to be released can be directly used as monomers and be incorporated in the main chain of the polymer. This is the case for instance of *p*-coumaric acid<sup>24</sup> or morphine<sup>25</sup> that were used to form biodegradable poly(anhydride-ester) (Fig. 4a-b) with AMI of 69 and 52%, respectively. If the drug possesses only one reactive group for polycondensation as it is the case for the anti-inflammatory drugs naxopren (AMI = 62%) and ibuprofen (AMI = 64%) that have one carboxylic acid functionality, they can be grafted as pendant groups in the side-chain of polyesters (Fig. 4c).<sup>26</sup>

The AMI number can be also significantly increased by grafting the drugs on the side-chains of polymers. Up to 43 wt.% of paclitaxel could be introduced in the side-chain of the polyacrylic acid segment of a block copolymer.<sup>27</sup> The polymers could self-assemble to nanoparticles in water and high antitumor activity was observed *in-vitro*. Another method is to use the drug as monomer in block copolymers that form nanoparticles in water. Thus, more than 50 wt.% of the drug camptothecin could be loaded in nanoparticles by using it as a monomer prodrug that can be cleaved by reduction.<sup>28</sup>

Interestingly, these strategies can be hence converted for preparing polymer nanocontainers that can release active substances during their degradation as shown in Fig. 2. L-Arginine, which can be employed for dentin hypersensitivity, was copolymerized by interfacial polyaddition in water-in-oil miniemulsions to form nanocapsules.<sup>29</sup> This means that the chemical encoding of active molecules can be further implemented into polymer nanocontainers. An example of a very efficient system was reported by Kwon et al.<sup>30</sup> Nanoparticles were formed with the polymer poly(vanillin oxalate). The particles could deliver the anti-inflammatory and antioxidant vanillin molecule after oxidation and acidification. An elegant approach is to create a drug-drug conjugate to form nanoparticles. The hydrophilic irinotecan and the hydrophobic chlorambucil, both anticancer drugs, were conjugated via a hydrolysable ester linkage.<sup>31</sup> The amphiphilic molecules were used to create nanoparticles, which displayed longer blood retention half-time compared to free drugs. This allowed for the accumulation of the prodrug in tumor tissues and the ester bond could be cleaved by hydrolysis after cellular internalization. Anticancer activity was demonstrated *in vitro* and *in vivo*.

Fig. 2

### Encoding the active agents for promoting co-release of multiple payloads from nanocontainers

The encoding of the active payload to be released in a polymer which forms the nanocontainers can be also used to release a second payload during the degradation of the nanocontainers. This approach was demonstrated by synthesizing amphiphilic copolymers with solubilizing units (polyvinylpyrrolidone) and units

bearing the functional molecules to be released (Fig. 4d).<sup>32</sup> The active payload was selected to be the corrosion inhibitor mercaptobenzothiazole that was bound with a disulfide linkage to the main chain of the copolymer. Nanoparticles were formed by self-assembly in water and were able to encapsulate an additional hydrophobic payload. The cleavage of the disulfide bonds led therefore to the simultaneous release of the corrosion inhibitor and second payload. The AMI could be tuned between 2 and 22%, depending on the ratio of monomers in the copolymer. Such an approach was also demonstrated in the case of large poly(anhydride-ester) microparticles based on salicylic acid. The anti-inflammatory drug salicylic acid could be released from the microparticles by hydrolysis, hereby triggering the release of encapsulated insulin.<sup>33</sup> The AMI calculated by taking into account the produced salicylic acid and the released insulin was 70%. In this case, the encapsulated insulin was distributed inside the monolithic polymer microparticles and not encapsulated in the core of a capsule.

The ratio of active molecules to be released can be substantially increased by employing the aforementioned strategy but designing the nanocontainers as core-shell nanoparticles with a functional liquid core instead of homogeneous monolithic nanoparticles.<sup>34</sup> For this, block and random copolymers bearing corrosion inhibitors in the side-chain were used to form nanocapsules with a liquid self-healing agent physically entrapped in the core of the nanocapsules (Fig. 3). The release of the corrosion inhibitors triggered a second release of the entrapped self-healing agent and the system could reach an AMI of 56%. The release rate could also be controlled by the structure of the copolymer, *i.e.* random or block.

**Fig. 3**

**Fig. 4**

## Perspectives

The systems proposed are still far away to be fully developed and many interesting properties could be implemented in new nanocontainers to increase their efficiency and AMI value. The ideal nanocontainers would have an AMI value of 100% meaning that all material forming the shell can be degraded to useful and active molecules (Fig. 2). The liquid core and the shell would therefore need to be degraded to form functional molecules. The functional molecules can be either chemically attached to the core or shell or physically bound. Such a concept is not only applicable for nanocontainers but also to other types of nanomaterials. The design could be combined with the self-immolative concept<sup>35</sup> so that the degradation could be accelerated upon demand. For biomedical applications, the concept could be also married with photodynamic therapy,<sup>36-37</sup> so that part of the degraded material becomes phototoxic while the rest of the degraded material is active but non-toxic. Indeed, toxicity issues in circulation and *in vivo* continue to be a major issue that need to be carefully investigated

before a product is approved for human trial. Finally, this approach could be employed to release very fragile or reactive ingredients as it is the case in biology. For instance, preprohormones are produced in the body to protect hormones such as vasopressin that possess a very low life time.<sup>38</sup>

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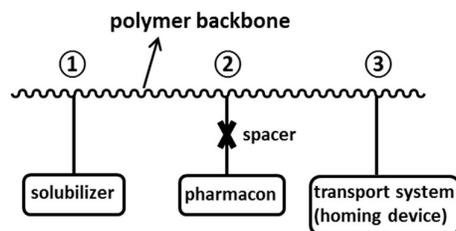
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## MINIREVIEW

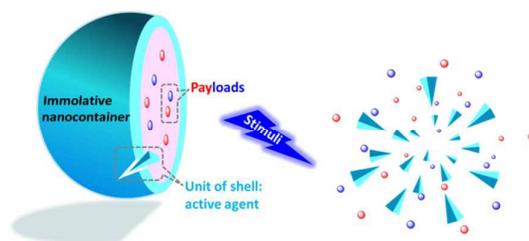
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## FIGURES



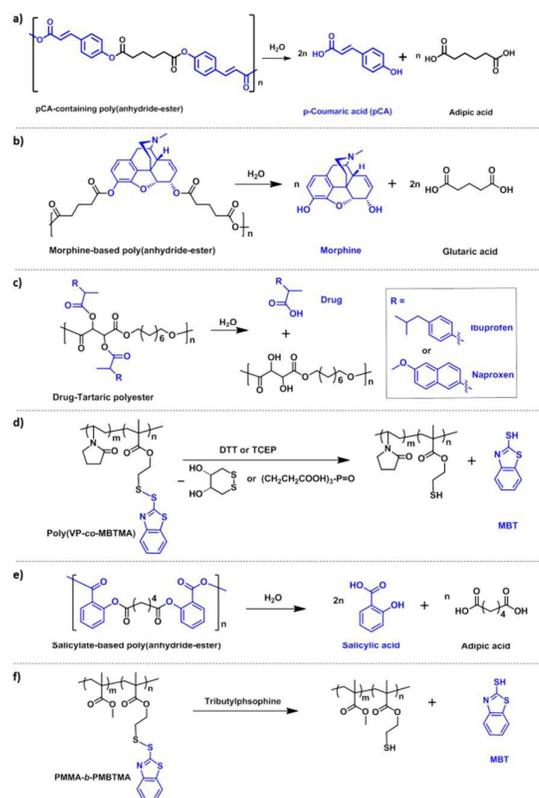
**Fig. 1** Model of a pharmacologically active polymer. Adapted from reference 16.



**Fig. 2** Scheme of the nanocontainers with encoded active substances that are released during their degradation.



**Fig. 3** AFM and SEM images of block copolymer nanocapsules with corrosion inhibitors chemically encoded in the shell for a triggered release of both the corrosion inhibitor and a liquid self-healing agent present in the core of the nanocontainers.<sup>34</sup>



**Fig. 4** Examples of copolymers with active molecules (marked in blue) as pendant groups in their main chains or side chains showing release of these active molecules after cleavage of corresponding bond.<sup>24-26, 32-34</sup>