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Nanoparticle-triggered release from lipid membrane vesicles

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Abstract

Superparamagnetic iron oxide nanoparticles are used in a rapidly expanding number of research and practical applications in biotechnology and biomedicine. We highlight how recent developments in iron oxide nanoparticle design and understanding of nanoparticle membrane interactions have led to applications in magnetically triggered, liposome delivery vehicles with controlled structure. Nanoscale vesicles actuated by incorporated nanoparticles allow for controlling location and timing of compound release, which enables e.g. use of more potent drugs in drug delivery as the interaction with the right target is ensured. This review emphasizes recent results on the connection between nanoparticle design, vesicle assembly and the stability and release properties of the vesicles. While focused on lipid vesicles magnetically actuated through iron oxide nanoparticles, these insights are of general interest for the design of capsule and cell delivery systems for biotechnology controlled by nanoparticles.

Introduction

Q2 Encapsulating drugs and vaccines has been shown to be highly beneficial for multiple reasons. A vesicle surrounded by an amphiphilic membrane allows incorporation of hydrophobic and amphiphilic drugs into the membrane while hydrophilic drugs can be stored in the aqueous interior [1]; the encapsulated cargo is protected from enzymatic degradation [2]. Furthermore, the surface functionality of the delivery vehicle can be modified to target them to certain locations [2–5]. Decreased degradation and in particular a high degree of localization of released cargo allows for use of much lower overall concentrations of the drug compared to systemic release. With this decrease in the injected and freely available drug dose, the risk of adverse side effects, e.g. toxicity or immune system reaction, is lowered [2,6]. Targeted release systems should ideally also allow for external control over timing and dose of the released cargo at the target location. There are also several biotechnological applications where externally controlled triggered release vehicles might serve as useful tools. Delivery of compounds, more efficient transfection mechanisms, poration of cells and even artificial organelles incorporated into cells are all possible applications that go hand in hand with a greater understanding of membrane release mechanisms.

Nanoparticles are increasingly researched as functional components in hybrid materials, where the integration of the nanoparticle with its matrix is key. An emerging such set of applications is the use of nanoparticles to control permeability of membranes and in particular vesicles. Many nanoparticles have unique properties allowing them to localize response, e.g. in the form of heat, to optic, electric and magnetic fields. They can therefore be used to control the properties of drug delivery structures, such as stealth liposomes, on the nanoscale; such systems and their applications have received much attention and been the subject of several recent reviews [7–9]. However, such applications put tremendous demand on nanoparticle stability at physiological conditions, close control over nanoparticle size and controlled surface presentation of functionalities.

Controlling the release rate of compounds from the vesicle in response to a change in the local environment actuated by a

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nanoparticle provides a great opportunity to optimize systems for biomedical release applications. Importantly, such constructs can circumvent the typical problem of having to balance low passive permeability (leakage) against high release efficiency for thermally activated release vehicles. The enabled externally triggered release at a controlled location and time point allows the use of very potent drugs, since the interaction with the right target is ensured. In extension, by varying the trigger particle, it can enable the sequential release of multiple drugs at controlled dosage; a major goal of personalized or nanomedicine could thereby be reached. The focus of this short review is in particular the magnetically triggered release of nanoparticle containing liposomes; what is known about the assembly of such vesicles and their optimization.

Stabilization of core–shell nanoparticles: Example of superparamagnetic iron oxide nanoparticles

Although a variety of inorganic, metal and oxide, nanoparticles are considered and tested for biomedical and biotechnological applications, superparamagnetic iron oxide nanoparticles have distinct advantages such as very low toxicity (Lewinski et al., Q3 2008; Weissleder et al., 1987) [10] and interaction with magnetic fields that penetrate biological environments [8]. Therefore, iron oxide nanoparticles are used in a rapidly expanding number of research and practical applications in the biomedical field [11]

Nanoparticles will rapidly aggregate without a dispersant shell through interactions between themselves or through interactions with biological molecules. The result of aggregation is disruption of structure, loss of function and precipitation. For the grafted dispersant shell to prevent aggregation it has to fulfill a minimum of important criteria: (i) be densely grafted; (ii) have sufficient thickness to screen interactions with the core; and (iii) be irreversibly grafted to the inorganic core surface also during extreme dilution and heating during actuation [11]. Grafting of dispersants refers to their binding to the inorganic NP surface. By covalently binding a high-affinity anchor to the end of a linear dispersant molecule a well-defined adsorption geometry to the nanoparticle surface can be achieved that fulfills these requirements, which are tantamount to colloidal stability. The resulting core–shell nanoparticles can be divided into four components: core, anchor, spacer and optional surface functionalities (Fig. 1). Each of these components can independently be adjusted through modular build-up starting from dispersants grafted to the nanoparticle interface. The resulting defined geometry renders such nanoparticles very versatile for a multitude of applications [11–13]; it is now realized to be especially crucial for the application to nanoparticle-actuated capsules [8].

Nanoparticle actuated vesicle release systems

The assembly and characterization of drug delivery systems has been the subject of many studies with an increasing number dealing with smart, bioinspired, nanoscale carriers [14,15] This tremendous scientific interest is closely related to commercial demand for stable, smart, nanoscale capsules that can easily and cost effectively be assembled in a versatile way with controlled release properties. Recent advances in application of nanoparticles to control drug release from vesicles build on new tools for controlling the architecture, colloidal stability and functionality of iron oxide, but also gold, nanoparticles.

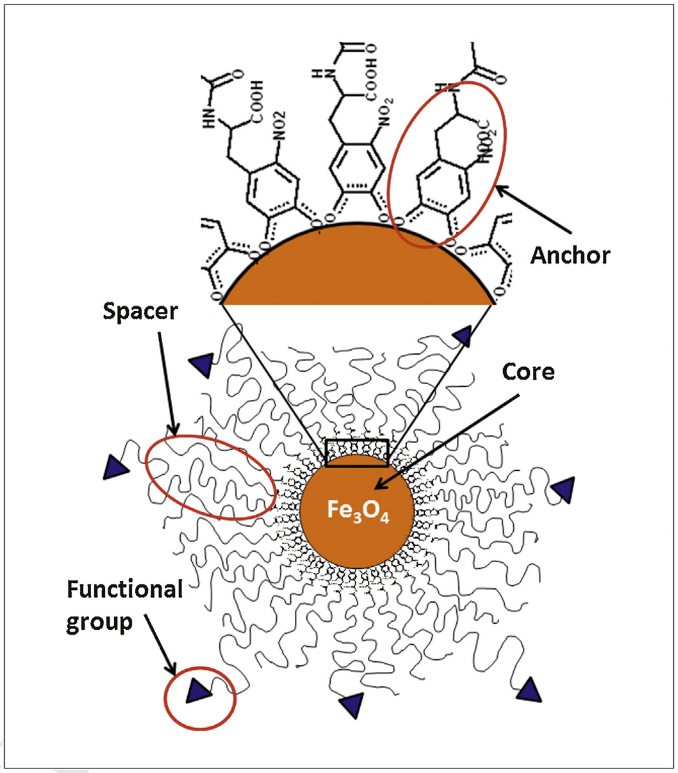

FIG. 1

Nanoparticles stabilized with irreversibly binding low M_W dispersants result in a defined core–shell structure. Such NPs can be divided into four components: core, anchor, spacer, and end-functional group, which can be optimized for the desired function in parallel. The trigger function in the core can therefore be made independent on the vesicle interaction of the shell.

Using nanoparticles as actuators to control release in drug delivery vehicles require embedding of the nanoparticle into the drug containing structure. Particularly elegant constructs are nanoscale vesicles that contain nanoparticles as part of the structure as drug delivery containers (Fig. 2). Superparamagnetic nanoparticles have some advantages for delivery applications in dense biological media compared to the more commonly proposed use of plasmonic metal nanoparticles. Magnetic fields penetrate and are relatively benign to tissue, but can interact strongly with magnetic nanoparticles even smaller than 10 nm [8]. Light with longer wavelength than near infrared light cannot penetrate into tissue or other biological samples; metallic nanoparticles resonantly interacting with NIR light require at least one dimension larger than 100 nm; such large size severely impacts their application, but can be circumvented by combining the metal nanoparticle with a sufficiently dense dielectric layer, either as a core or as coating that shifts the resonance [16,17]. Magnetically labeled drug delivery vehicles further can be used as magnetic resonance imaging contrast agents for theranostic applications where imaging/diagnostics and triggered release are combined [11].

One of the most common ways to control the release rate of compounds from delivery vehicles is to make use of a thermally driven change in permeability or solubility. For example, lipid vesicles display highly increased permeability to small compounds around the membrane melting temperature (T_m) [18,19]. Also amphiphilic block copolymers as well as hydrogel particles can

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