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Artificial swarming: Towards radiofrequency control of reversible micro-particle aggregation and deposition

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ABSTRACT

The ability to undergo a transition between dispersed or single-cellular state and aggregated or multi-cellular state provides distinct evolutionary advantages to many natural organisms. Due to a change of hydrodynamic diameter over several orders of magnitude and associated change of fluid–particle interaction (settling velocity) or intra-particle transport phenomena (heat transfer and/or diffusion) that typically scales with the square of the particle size, radically different behaviour can be achieved in terms of transport in a fluid environment, sourcing nutrition, escaping predators or maintaining homeostasis. In this work we report on the implementation of an artificial system that is able to undergo a reversible transition between dispersed and aggregated state, using the principles of "remote control" by radiofrequency (RF) signals. The individual artificial cells are represented by hollow-core SiO_2/Fe_3O_4/PNIPAM microparticles with a stimuli-responsive porous shell that possess the following functionalities: *(i)* RF-induced local particle heating, due to the presence of superparamegnetic nanoparticles in the structure; *(ii)* temperature switchable storage/release functionality due to a combination of hollow-core porous silica skeleton with a PNIPAM layer; and *(iii)* temperature switchable aggregation, due to the hydrophilic/hydrophobic transition of the PNIPAM layer. The combination of RF-switchable aggregation and temperature-responsive release kinetics of a lipophilic substance makes it possible to trigger particle aggregation and deposition remotely, and thus control the release kinetics of encapsulated payload in both time and space.

1. Introduction

While the radiofrequency (RF) control of mechatronic systems is ubiquitous in daily life and technology, the ability to remotely control molecular or colloidal systems using RF signals has so far been exploited rather scarcely. To achieve remote control of a chemical system, at least two conditions must be met: *(i)* the system has to be stimuli-responsive in some way, and *(ii)* there must exist a means of executing the stimulus without direct physical intervention with the chemical environment. Stimuli-responsive chemical systems—i.e. systems able to dynamically respond to changes in the physico-chemical properties of their microenvironment—can be traced back to the concept of thermo-sensitive liposomes [1]. Since then, numerous other chemical systems responsive to various endogenous or exogenous stimuli have been described. Examples of endogenous stimuli include pH-sensitive drug-delivery systems [2], redox-sensitive systems [3] and enzyme-sensitive nanocarriers [4]. Exogenous stimuli such as ultrasound [5], light of a specific wavelength [6], or magnetic field [7–9] have been reported.

Thermo-responsive systems can have the form of microgels, vesicles, polymer brushes or other structures containing a material exhibiting a phase transition at a given temperature [10]. The phase transition then leads to a step change in a macroscopically observable property such as solubility, permeability, conductivity or wettability of the system. For example, the polymer poly-N-isopropylacrylamide (PNIPAM) exhibits a lower critical solution temperature (LCST), meaning that it is hydrophilic at temperatures below approx. 32 °C but changes its character to hydrophobic above this temperature. Temperature cycling can then lead to phenomena such as shrinking-swelling behaviour of a gel [11,12] or the change in activity of cell-penetrating peptides [13]. The remote control of thermoresponsive systems requires that a local temperature change can be achieved at some distance without physical contact with the system. This is in principle possible by including an additional component into the system (i.e., a susceptor), liable to remote triggering by energy in other forms than heat. For instance, stimuli realized by electromagnetic field in the form of near-infrared (NIR) photo-thermal energy [14], inductively coupled magnetic (ICM) field [15] or radiofrequency (RF) field [16] have been already demonstrated to induce heating of metallic nanoparticles and consequently deliver targeted hyperthermia.

However, non-invasive NIR irradiation is often limited by its low penetration depth [17] and ICM field by the applicable magnetic field

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strength and difficulty in particle targeting [15]. In contrast, RF heating of superparamagnetic iron oxide nanoparticles (SPIONs) offers several advantages, such as high penetration depth and acceptable safety profile, since no harmful effects have been reported on humans even after several hours of exposure to the RF field [18]. Furthermore, SPIONs act as an exceptional contrast agent in magnetic resonance imaging (MRI), as they significantly enhance contrast in signal intensity without compromising its stability [19]. This enables both sensing and actuation functionality.

In our earlier work, RF-induced heating of metal or metal oxide nanoparticles has been applied for the controlled release from composite silica microparticles [20,21], controlled diffusion from hydrogel sponges [22] or controlled desorption from composite adsorbents [23]. Recently, RF signals have also been used for controlled release from magnetic liposome microgels [24] and for the remote control of an enzymatic reaction [25]. While these works have demonstrated the ability to control the *timing* of cargo release from particulate carries, an equally important aspect relates to the *location* of the release. In low Reynolds number flows, the particle relaxation time is proportional to the square of the particle size according to

$$\tau_{St} = \frac{\rho_p d_p^2}{18\mu} \tag{1}$$

where τ_{St} [s] is the relaxation time (i.e., the characteristic time needed for the particle to achieve its terminal velocity relative to the fluid), ρ_p [kg m^{-3}] is the particle density, d_p [m] is the particle hydrodynamic diameter, and μ [Pa s] is the dynamic viscosity of the fluid. The value of the relaxation time has a direct influence on the probability of particle capture during flow over obstacles or in a porous medium. Hence, a change of the hydrodynamic particle diameter via aggregation would appear to be an effective mechanism of controlling particle deposition.

The aim of the present work, therefore, was to design and synthesize colloidal particles capable of RF-controllable aggregation, to characterize them and to demonstrate their functionality. The particle design is based on hollow SiO_2/Fe_3O_4/PNIPAM composite microparticles with a specific structure that enables each component to contribute a specific function to the system as a whole: hollow SiO_2 microparticles provide a structural support as well as storage/release function, incorporated iron oxide nanoparticles act susceptors for radiofrequency heating, and finally, grafted PNIPAM chains provide stimuli-responsive surface functionality in the form of temperature-dependent transition between hydrophilic and hydrophobic character. This paper is structured as follows: the particle synthesis procedure and experimental methods will be described first, followed by a discussion of the effect of synthesis conditions on the particle properties (composition, stability). Finally, the particle functionality—namely radiofrequency heating, temperature-dependent diffusion, and reversible aggregation—will be demonstrated.

2. Experimental methods

2.1. Materials

Polyvinyl-pyrolidone (PVP, M_W = 55 000, Sigma Aldrich), 4,4-azobis(4-cyano-valeic acid) (ABCVA, 75%, Sigma Aldrich), styrene (>99.5%, Fluka), deionized water, ethanol for UV spectroscopy (>99.8%, Penta), toluene (99%, Lachner), tetraethyl orthosilicate (TEOS, >99%, Fluka), ammonia aqueous solution (25 wt.%, Penta), 3-(trimethoxysilyl)propyl methacrylate (3-MOP, ≥98%, Sigma Aldrich), *N*-isopropylacrylamide (NIPAM, ≥99%, Sigma Aldrich), *N,N′*-methylene-bis(acrylamide) (MBA, ≥99.5%, Fluka), potassium peroxodisulfate (KPS, ≥99%, Sigma Aldrich), *N,N,N′,N′*-tetramethylethane-1,2-diamine (TEMED, ~99%, Sigma Aldrich), aqueous dispersion of citrate magnetite nanoparticles (5.0 g/l [26]), Nile Red (≥98%, Sigma Aldrich), SYLGARD® 184 Silicone Elastomer Kit (Dow Corning), sodium hydroxide (NaOH, Penta), potassium peroxodisulfate (KSCN, >99%, Fluka), and hydrochloric acid (HCl, 35%, Penta).

2.2. Synthesis of SiO_2/Fe_3O_4/PNIPAM microparticles

The microparticles were synthesized in several steps as shown schematically in Fig. 1. First, hollow silica spheres with incorporated magnetite nanoparticles were prepared using the solid template method [27]. PVP-modified polystyrene particles with a mean diameter of 1.0 μm were used as templates, from which SiO_2/PS/Fe_3O_4 microparticles were obtained using a modified Stöber method. During this process, Fe_3O_4 nanoparticles were gradually incorporated into the growing silica seeds, resulting in the formation of a porous SiO_2/Fe_3O_4 shell (mean pore diameter approx. 40 nm) on the surface of the PVP-modified PS templates. In order to obtain the final SiO_2/Fe_3O_4/PNIPAM microparticles, the SiO_2/Fe_3O_4 intermediate product was functionalized by introducing a double bond onto its surface using 3-(trimethoxysilyl)propyl methacrylate (3-MOP) [28] and the polystyrene core was then removed by dissolution in toluene. The functionalization allowed PNIPAM to be grafted onto the particles as a result of radical copolymerization of 3-MOP modified SiO_2 with NIPAM. The details and conditions of the individual steps were as follows:

Step 1: Preparation of PVP-modified PS templates. PVP (1.5 g), ABCVA (0.2 g), H_2O (5.0 g) and ethanol (22.5 g) were charged into a 100 ml flask with magnetic stirring (400 rpm). The reaction solution was deoxygenated by bubbling nitrogen at room temperature for 30 min and then heated to 70 °C for 1.5 h. Styrene (5.0 g) and ethanol (22.5 g) were added to the system and the reaction was allowed for 6 h (400 rpm, nitrogen atmosphere, reflux). The PS particles were collected by centrifugation (8000 rpm, 5 min), washed by ethanol 3 times and dispersed in 300 ml of ethanol for UV as stock solution.

Steps 2–3: Preparation of PS/SiO_2/Fe_3O_4 microparticles. 10 ml of the stock solution prepared in Step 1 was added to a mixture containing 30 ml of ethanol, 3 ml of aqueous dispersion of citrate-stabilized magnetite nanoparticles (4.7 g/l) and TEOS (1 ml). The mixture was then slowly heated to 50 °C in an oil bath, with magnetic stirring (500 rpm). A solution of ammonia (2.5 ml, 25% in H_2O) was then added quickly and the reaction was terminated after 25 min. The resulting PS/SiO_2/Fe_3O_4 microparticles were removed from the solution by centrifugation (6500 rpm, 5 min) and washed by ethanol 3 times.

Steps 4–5: Preparation of functionalized of SiO_2/Fe_3O_4 microparticles. Particles produced in Step 3 were dispersed in a mixture of ethanol (12 ml), demi water (1.2 ml), ammonia aqueous solution (1 ml) and 3-MOP (0.1 g). The solution was left on a magnetic stirrer for 48 h (600 rpm, room temperature) and then centrifuged (6500 rpm, 5 min), re-dispersed in 10 ml of ethanol and transferred to a flask containing 40 ml of toluene. After stirring for 1 h, the obtained particles were centrifuged 3 times (same conditions), washed by ethanol and finally dispersed in 40 ml of demi water to form a 0.5 wt.% suspension.

Step 6: Preparation of SiO_2/Fe_3O_4/PNIPAM microparticles. 40 ml of functionalized SiO_2/Fe_3O_4 microparticles stock solution (0.5 wt.%) was charged into a 50 ml flask. After that, 3.0 g of aqueous solution containing NIPAM (0.2 g) and MBA (0.03 g) was added into the flask and the reaction mixture was deoxygenated by bubbling nitrogen for 30 min, followed by slow heating to a set temperature (25 °C, 40 °C or 70 °C) under magnetic stirring at 500 rpm, reflux, and nitrogen atmosphere. After reaching the reaction temperature, 2.0 g of aqueous solution of KPS (0.005 g) was transferred to the flask by a syringe and the reaction was allowed to proceed for a set time (1 h, 2 h, 3 h, and 15 h). The