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pH-Dependent silica nanoparticle dissolution and cargo release

Giorgia Giovaninni[a,2], Colin J. Moore[b,*,1], Andrew J. Hall[a], Hugh J. Byrne[b], Vladimir Gubala[a]

[a] Medway School of Pharmacy, University of Kent, Central Ave, Chatham Maritime, Kent, ME4 4TB, United Kingdom
[b] FOCAS Research Institute, Dublin Institute of Technology, Kevin St., Dublin 8, Ireland

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ABSTRACT

The dissolution of microporous silica nanoparticles (NP) in aqueous environments of different biologically relevant pH was studied in order to assess their potential as drug delivery vehicles. Silica NPs, loaded with fluorescein, were prepared using different organosilane precursors (tetraethoxysilane, ethyl triethoxysilane or a 1:1 molar ratio of both) and NP dissolution was evaluated in aqueous conditions at pH 4, pH 6 and pH 7.4. These conditions correspond to the acidity of the intracellular environment (late endosome, early endosome, cytosol respectively) and gastrointestinal tract ('fed' stomach, duodenum and jejunum respectively). All NPs degraded at pH 6 and pH 7.4, while no dissolution was observed at pH 4. NP dissolution could be clearly visualised as mesoporous hollows and surface defects using electron microscopy, and was supported by UV–vis, fluorimetry and DLS data. The dissolution profiles of the NPs are particularly suited to the requirements of oral drug delivery, whereby NPs must resist degradation in the harsh acidic conditions of the stomach (pH 4), but dissolve and release their cargo in the small intestine (pH 6–7.4). Particle cores made solely of ethyl triethoxysilane exhibited a 'burst release' of encapsulated fluorescein at pH 6 and pH 7.4, whereas NPs synthesised with tetraethoxysilane released fluorescein in a more sustained fashion. Thus, by varying the organosilane precursor used in NP formation, it is possible to modify particle dissolution rates and tune the release profile of encapsulated fluorescein. The flexible synthesis afforded by silica NPs to achieve pH-responsive dissolution therefore makes this class of nanomaterial an adaptable platform that may be well suited to oral delivery applications.

1. Introduction

Nanoparticle (NP)-based delivery systems have come to prominence over the past two decades as they can be designed to carry poorly soluble drugs or molecules that are prone to degradation in biological conditions [1–4]. NPs can also transport therapeutics across highly regulated biological boundaries such as the blood brain barrier [5,6]. In particular, silica NPs (SiNPs) are regularly described as excellent candidates for drug delivery applications because they are regarded as biocompatible [7–10] and inert [11]. However, it is the adaptable and flexible nature of siloxane chemistry that makes this class of nanomaterial so widely studied as a drug delivery agent. This is facilitated, in part, by the large number of commercially available organosiloxane derivatives that can be used as precursors for SiNP synthesis. The chemistries of these precursors can vary widely and means that SiNPs can exhibit a range of useful physicochemical properties (e.g. different porosity, charge, hydrophobicity), which, in turn, allows for different kinds of therapeutics to be encapsulated and delivered to disease sites.

Most silica-based drug delivery studies employ mesoporous silica, having pore sizes of the order 2–50 nm, and rely on tunable cargo release via a 'gatekeeper' strategy [9,12–15]. Despite their popularity, the requirement to load cargo and incorporate gatekeepers after NP synthesis introduces additional complexity to particle design. On the other hand, microporous silica NPs have characteristic pores of less than 2 nm [16], that are challenging to characterise accurately with appropriate methods and expertise compared to mesoporous silica [17]. Encapsulatation of different therapeutics can be achieved during NP synthesis [2,18,19] and the release mechanism is via the natural degradation of the silica [20]. The process of NP degradation is therefore largely governed by the organosiloxane precursors, and their associated physicochemical properties, that can be easily imparted during synthesis. However, microporous silica remains understudied as a drug delivery candidate and is more frequently reported in immunoassays [21–23] and bioimaging [10,24–26]. This is surprising, considering the

* Corresponding author.
E-mail addresses: giorgia.giovannini@iit.it (G. Giovaninni), colin.moore@univ-tours.fr (C.J. Moore), a.hall@kent.ac.uk (A.J. Hall), hugh.byrne@dit.ie (H.J. Byrne), v.gubala@kent.ac.uk (V. Gubala).
[1] Current address: EA 6295 Nanomedicine and Nanoprobes, Faculty of Pharmacy, University of Tours, 31 avenue Monge, Tours 37200, France.
[2] Current address: Istituto Italiano di Tecnologia (IIT), Via Morego 30, Genoa, 16163, Italy.

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adaptable nature of silica and the fact that it, in comparison to its mesoporous counterpart, avoids the need for gatekeeping to control drug release and the associated complications related to cargo leeching. We therefore feel microporous silica NPs are an interesting nanomaterial to study and have the potential to impact the drug delivery field.

We hypothesise the development of a dissolution-based method of controllably releasing encapsulated cargo from microporous SiNPs by synthesising colloids using different organosiloxane precursors. SiNPs are formed utilising hydrolysis but this pH-dependent mechanism is reversible and suggests SiNPs may degrade at different rates in different acidic conditions.

Intracellular NP-drug delivery typically requires endocytosis of the nanocarrier to transport a therapeutic across the cell membrane. Trafficking of the NPs from the extracellular environment (pH 7.4) into early endosomes (pH 6) and then to late endosomes/lysosomes (pH 4) means environments of different acidity are experienced. The same can be said for oral drug delivery applications in which medicines first encounter the harsh environment of the stomach (pH 4 in 'fed state') and are then passed to the duodenum (pH 6) and jejunum (pH 7.4) for adsorption.

We have synthesised core-shell SiNPs via the reverse microemulsion method (Fig. 1) and investigated their dissolution in aqueous conditions at biologically relevant pH (pH 4, pH 6, pH 7.4), similarly to other NP dissolution studies [27–30]. Different siloxane precursors were employed during the core formation in order to produce particles that exhibit varying degrees of hydrophobicity, which in turn may be able to affect NP dissolution and the ability to host different cargos. A shell composed of tetraethoxysilane (TEOS) and negatively charged phosphonates was then added to each set of particles to insure similar surface chemistry.

The precursors used for core formation were TEOS, ethyl triethoxysilane (ETOS), bis(triethoxysilyl)benzene and bis(triethoxsilyl) biphenyl. However, the colloids formed using the aromatic oxysilanes were unstable in aqueous conditions and only particles formed using TEOS and ETOS were studied to assess dissolution. Degradation and release of the encapsulated cargo (i.e. fluorescein; FITC) from the SiNPs were monitored by electron microscopy and fluorimetry (Fig. 2), and stability studies were carried out using dynamic light scattering (DLS). Overall, negligible dissolution was observed at pH 4 and suggested the NPs may survive the acidic conditions of the stomach or cellular lysosome, thus minimising cargo release. NP degradation was accelerated in pH 6 and pH 7.4 and may support the release the encapsulated cargo in small intestinal pH, at physiological pH or in early endosomes. A study mimicking progress through the GI tract (i.e. pH 4 to pH6 to pH 7.4) then showed the NPs released fluorescein in a pH-dependent manner, with NPs formed using more ETOS exhibiting 'burst' release profiles and those formed solely using TEOS displaying 'slow' release.

2. Methods

2.1. NPs synthesis and characterisation

Materials, procedures, size and ζ-potential analysis, TEM studying of NP dissolution are detailed in the Supporting Information.

2.2. FITC-release assay

The degree of FITC release was evaluated by measuring the amount of dye present in the supernatant and comparing the values measured with the fluorescent-based calibration curve for FITC at the corresponding pH. The values achieved from the independent experiments are reported as average (n = 3) ± SD. A Tecan Infinite M200 Pro

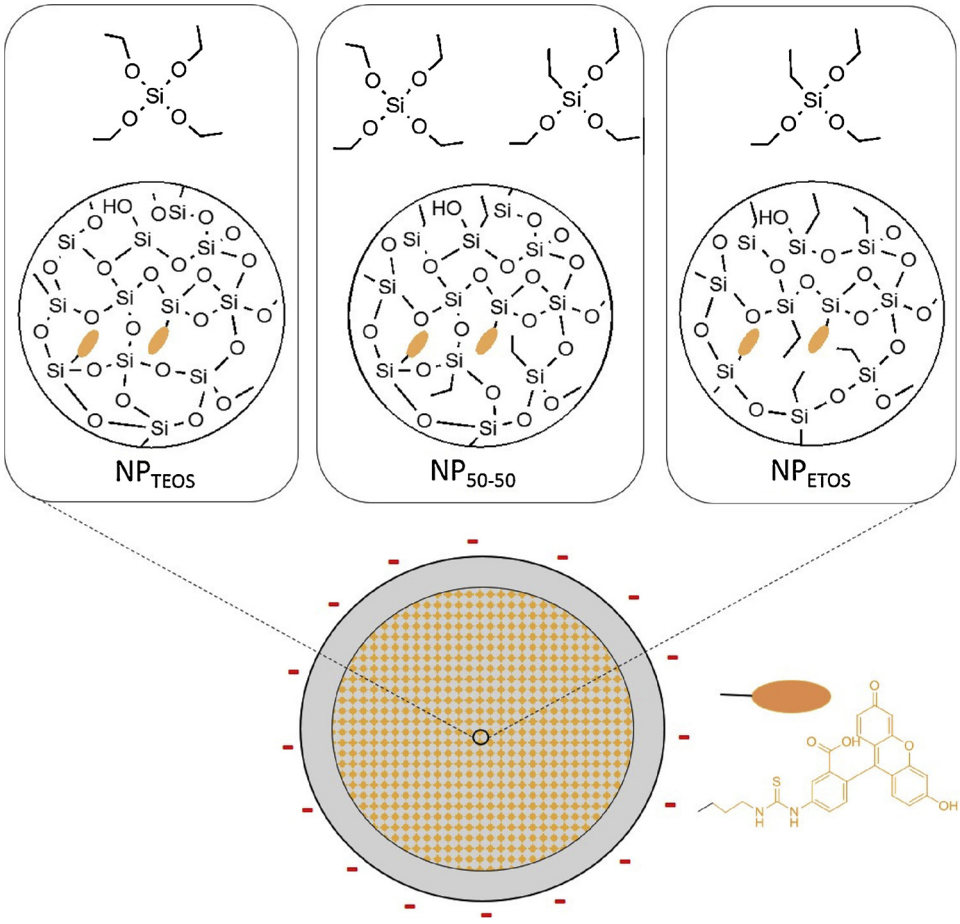

Fig. 1. Silica NPs were prepared with different core chemistries by employing different NP precursors during synthesis: tetraethoxysilane (TEOS) or ethyl triethoxysilane (ETOS). These NPs were called NP_{TEOS} and NP_{ETOS}. TEOS and ETOS were also added in an equal molar ratio (NP_{50-50}). Covalently binding fluorescein (FITC) in the NP cores also provided information about particle degradation and cargo release.