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Spray drying of silica microparticles for sustained release application with a new sol-gel precursor

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ABSTRACT

A new precursor, tetrakis(2-methoxyethyl) orthosilicate (TMEOS) was used to fabricate microparticles for sustained release application, specifically for biopharmaceuticals, by spray drying. The advantages of TMEOS over the currently applied precursors are its water solubility and hydrolysis at moderate pH without the need of organic solvents or catalyzers. Thus a detrimental effect on biomolecular drug is avoided. By generating spray-dried silica particles encapsulating the high molecular weight model compound FITC-dextran 150 via the nano spray dryer Büchi-90, we demonstrated how formulation parameters affect and enable control of drug release properties. The implemented strategies to regulate release included incorporating different quantities of dextrans with varying molecular weight as well as adjusting the pH of the precursor solution to modify the internal microstructures. The addition of dextran significantly altered the released amount, while the release became faster with increasing dextran molecular weight. A sustained release over 35 days could be achieved with addition of 60 kD dextran. The rate of FITC-Dextran 150 release from the dextran 60 containing particles decreased with higher precursor solution pH. In conclusion, the new precursor TMEOS presents a promising alternative sol-gel technology based carrier material for sustained release application of high molecular weight biopharmaceutical drugs.

1. Introduction

The sol-gel technology is presently believed to be one of the most promising approaches for controlled drug release (Avnir et al., 2006; Trewyn et al., 2007; Radin et al., 2009; Klouda, 2015). Its main advantage lies in the fact that the entrapment of drugs in a porous network proceeds without formation of covalent linkages between drug molecules and matrix (Avnir et al., 2006). As a result, the drug payload is intact, which is specifically important for biomolecular drugs like proteins (Avnir et al., 1994; Santos et al., 1999; Radin et al., 2001; Moreno et al., 2014; Censi et al., 2015; Ishii et al., 2016). Additionally, entrapment in a nanostructured amorphous glass matrix can support the long-term and thermal stability of proteins (Avnir et al., 2006; Censi et al., 2015; Ishii et al., 2016; Akash et al., 2014).

The sol-gel processing includes the use of a precursor, often metal or silicon alkoxides. When an alkoxide is mixed with water, it experiences hydrolysis and the products are involved in condensation reactions leading first to a sol formation followed by cross-linking of sol particles which causes the sol-gel transition and consequently porous network formation (Brinker and Scherer, 2013; Pierre, 2013). The silica sol-gel process is strongly influenced by additives such as short-chain alcohols (Ivanova et al., 2000), electrolytes (Zheng et al., 2003), and hydrophobic solubilizates (Aramaki et al., 2001). Silica as a carrier matrix exhibits several advantages over metal alkoxides, as it is relatively cheap and easy to purify, with excellent physical and chemical stability, good biocompatibility, and biodegradability with favorable tissue responses *in vitro* and *in vivo* (Radin et al., 2005; Peterson et al., 1998; Kortesuo et al., 2001a). Thus, silica-based sol-gel materials are frequently used for drug delivery purpose (Avnir et al., 2006).

Although sol-gel silica materials have many advantages for controlled drug release application, there still exist some disadvantages. Conventional silica precursors such as tetramethoxysilane (TMOS) and tetraethoxysilane (TEOS) are insoluble in water. In order to achieve a uniform sol, an organic solvent or surfactant is added and extreme conditions of pH and high temperature are required, which are unfavorable for the encapsulation of biomolecular drugs (Shchipunov, 2003). Furthermore, in the course of the reaction process, short-chain alcohols such as methanol or ethanol as by-products of the hydrolysis of tetraalkyl orthosilicates are generated, which negatively impact biomolecule resulting in unfolding and aggregation and subsequently

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restricts their use (Sattler et al., 1998). Although some biopharmaceutical-compatible methods have been reported based on the use of those precursors, evaporation of generated alcohol prior to biopharmaceutical entrapments and the necessity to use two different pH values (low pH for hydrolysis and neutral pH for entrapment) cannot be avoided (Santos et al., 1999; Teoli et al., 2006; Catauro and Bollino, 2014; Jun et al., 2011). Some solid-state silane precursors on the basis of glycerated silanes such as polyglycerylsilicate (PGS) or diglycerylsilane (DGS), are also investigated to entrap protein drugs since they are soluble in water at physiological pH and the residuals can be either removed or retained. However, they have high viscous solution, complicated procedure and insufficient porosity, which limit their usage in real practice (Kwon1 et al., 2013). In contrast, tetra(2-hydroxyethyl) orthosilicate (THEOS) has been investigated to address the solubility, temperature and pH problems associated with TEOS and TMOS (Shchipunov et al., 2004). Moreover, it is known that ethyleneglycol which is produced during THEOS hydrolysis has little effect on surfactant self-assemblies and phase behavior compared to methanol or ethanol (Shchipunov, 2003; Sattler et al., 1998; Shchipunov et al., 2004; Meyer et al., 2002; Shchipunov et al., 2005a; Shchipunov et al., 2005b). However, THEOS alone does not cause the jellification of water at ambient conditions over a period of a month. Additives such as polysaccharides are necessary to trigger the sol-gel processes (Shchipunov et al., 2005b).

Those problems may be circumvented by changing the ethoxy, methoxy or ethylene glycoxy groups of the precursor against ethylene glycol monomethylether (EGMM). EGMM with boiling point 124.5 °C is readily removed accompanying the water evaporation. As we found, this new precursor tetrakis (2-methoxyethyl) orthosilicate (TMEOS) is water soluble and the time of water jellification can be controlled from a few minutes to a few hours by adjusting the pH value between pH 6.0 to 8.0 without the need for additives at room temperature. Furthermore, hydrolysis renders longer chain alcohol which can be expected to show better compatibility with sensitive protein drugs. In the present study, the compatibility of ethylene glycol monomethylether (EGMM) as a by-product produced in course of TMEOS hydrolysis was checked with sensitive IgG1 antibody. Then the effects of pH and ionic strength on TMEOS gelation were examined. A nano spray dryer Büchi-90 was used to produce silica gel microparticles for release application. Prior to protein drug loading, FITC-dextran 150 (FITC-Dx 150) was used as a high molecular weight model compound to regulate the drug release kinetics. Dextrans of different molecular weight were incorporated into the silica microparticles. Additionally, the effect of several parameters such as silica/additive ratio, molecular weight of additives and pH of precursor solution were addressed.

2. Materials and methods

2.1. Materials

Tetrakis (methoxyethoxy) silane (TMEOS) was purchased from Suzhou Chum-Win New Material Science & Technology Co,. Ltd., Suzhou, China. Fluorescein isothiocyanate dextran 150 kDa (FITC:Glucose = 1:160) (FITC-Dx 150) was purchased from Sigma-Aldrich, Munich, Germany and Dextran 1 (Dx 1), Dextran 5 (Dx 5) and Dextran 60 (Dx 60) were purchased from Pharmacosmos A/S, Holbaek, Denmark. A 2 mg/mL IgG1 monoclonal antibody in 10 mM PBS pH 7.2 was used. Ethylene glycol monomethylether (EGMM, 99.5%) was supplied by the reagent center of the University of Munich, Germany. All other reagents used were of analytical grade. Deionized water (Milli-Q) was used for all precursor preparation.

2.2. Methods

2.2.1. Turbidity

The turbidity of IgG1/EGMM mixtures in formazine nephelometric units (FNU) was determined with a NEPHLA turbidimeter (Dr. Lange, Düsseldorf, Germany), based on light scattering in an 90 ° angle at λ = 860 nm. The system was calibrated with a formazine standard. Approximate 2 mL of each sample was used for analysis.

2.2.2. Light obscuration

Light obscuration tests were carried out according to Ph.Eur. 2.9.19. The particle counting of subvisible particles in a size range between 1 and 200 µm was conducted using a SVSS-C instrument and associated analysis software (PAMAS GmbH, Rutesheim, Germany). For each sample (n = 3) three measurements of a volume of 0.3 mL with a pre-run volume of 0.3 mL at fixed fill rate, emptying rate and rinse rate of 5 mL/min were performed. Prior to each measurement the system was rinsed with high purified water until particle counts of less than 30 particles/mL were determined. The obtained results represented the mean value of the particle counts of three measurements, referred to a sample volume of 1.0 mL.

2.2.3. High performance size exclusion chromatography (HP-SEC)

HP-SEC was performed on an Agilent 1100 series HPLC system (Agilent Technologies, Santa Clara, California, USA). The autosampler and the column were temperature controlled at 20 °C and 23 °C, respectively. The samples were centrifuged for 5 min at 2000 rpm. For each sample solution, 40 µl supernatant was injected onto a Tosoh TSKgel® G3000SWXL column (7.8 × 300 mm) (Tosoh Bioscience, Stuttgart, Germany) using a mobile phase of 100 mM sodium phosphate buffer with additional 100 mM sodium sulfate pH 6.8 at a flow rate of 0.5 ml/min. The eluted sample was detected by UV absorption at 280 nm. The chromatograms were analyzed regarding retention times and the area under the curve (AUC) with ChemStation® B.02.01-SR2 (Agilent Technologies).

2.2.4. Gelation time

0.6 mL TMEOS was mixed with 1.4 mL PBS between pH 6.0 and pH 8.0 at four different concentrations (10 mM, 30 mM, 50 mM and 200 mM). At designated time points, the mixtures were checked visually whether a gel had formed.

2.2.5. Particle preparation

To investigate the effects of additives, different formulations were prepared (Table 1). The total mass content of excipients was set to 5.5% (w/v). In a typical procedure, FITC-Dx 150 solution in 10 mM PBS was mixed with TMEOS to a final concentration of 0.05%. Hydrolysis was performed for 2 h. The spray drying conditions in the nano spray dryer Büchi-90 were T_{in}/T_{out}: 120 °C/58 °C, flow rate of drying air: 120 L/min, atomizing mesh size: 7.0 µm. Spray solutions were filtered through

Table 1
Formulations of precursors for spray drying.

Run number	TMEOS(SiO_2) (w/v)	Dextran (w/v)			pH
		1 kDa	5 kDa	60 kDa	
1	30%(5.5%)	0	0	0	6.0
2	27.5% (5.0%)	0.5%	0	0	6.0
3	25% (4.5%)	1.0%	0	0	6.0
4	20% (3.7%)	1.8%	0	0	6.0
5	10% (1.8%)	3.7%	0	0	6.0
6	27.5% (5.0%)	0	0.5%	0	6.0
7	25% (4.5%)	0	1.0%	0	6.0
8	20% (3.7%)	0	1.8%	0	6.0
9	10% (1.8%)	0	3.7%	0	6.0
10	27.5% (5.0%)	0	0	0.5%	6.0
11	25% (4.5%)	0	0	1.0%	6.0
12	20% (3.7%)	0	0	1.8%	6.0
13	10% (1.8%)	0	0	3.7%	6.0
14	25% (4.5%)	0	0	1.0%	6.2
15	25% (4.5%)	0	0	1.0%	6.4