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A redox strategy to tailor the release properties of Fe(III)-alginate aerogels for oral drug delivery

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ABSTRACT

Iron(III)-crosslinked alginate aerogel beads (d = 3–5 mm) were prepared and loaded with ibuprofen by using the technique of adsorptive deposition from supercritical CO_2. Additional formulations were prepared where the aerogels were co-impregnated by ibuprofen and ascorbic acid. The release of ibuprofen from the Fe(III)-alginate is much faster in pH = 7.4 (PBS) than in pH = 2.0 (HCl), which can be explained by the faster dissolution and higher swelling of the alginate matrix in PBS. By decreasing the size of the beads and using a higher G content alginate the release rate could be slightly increased. A marked acceleration of drug release was achieved in both HCl and PBS by incorporating ascorbic acid into the Fe(III)-alginate aerogel preparations. The explanation is that in aqueous media ascorbic acid in situ reduces the crosslinking Fe(III) to Fe(II). The latter does not interact strongly with alginate, which promotes the hydration of the chains, thus the erosion and dissolution of the carrier matrix.

1. Introduction

Highly porous aerogels can be relatively simply prepared from metal ion crosslinked alginate hydrogels (Garcia-Gonzalez, Alnaief, & Smirnova, 2011; Quignard, Valentin, & Di Renzo, 2008; Smirnova & Gurikov, 2017; Subrahmanyam, Gurikov, Dieringer, Sun, & Smirnova, 2015; Tkalec, Kranvogl, Uzunalic, Knez, & Novak, 2016). Similarly to the hydrogels, these aerogels are versatile biomaterials which were recently introduced into the field of drug delivery research (Garcia-Gonzalez et al., 2011; Veronovski, Novak, & Knez, 2012). The oral (Garcia-Gonzalez, Jin, Gerth, Alvarez-Lorenzo, & Smirnova, 2015; Mehling, Smirnova, Guenther, & Neubert, 2009) and mucosal (Goncalves et al., 2016) delivery applications of various active pharmaceutical ingredients, including fat-soluble vitamins (Pantic, Knez, & Novak, 2016) have been investigated. Layered (Veronovski, Knez, & Novak, 2013) and core-shell (Ulker & Erkey, 2014) formulations have also been developed aiming to fine-tune the release kinetics.

The timeframe of the dissolution of adsorbed drugs from alginate aerogel carriers heavily depends on the hydration, swelling and erosion of the matrix. Metal ion alginate gels readily dissolve in neutral or slightly acidic (pH > 5) solutions where the concentration of the crosslinking metal ion is low. In this case some of the coordination bonds break down, metal ions leach from the gel and alginate chains are hydrated. At pH < 4 alginate is protonated to alginic acid which forms a barely soluble layer on the surface of the particles limiting the overall rate of the degradation of the matrix (Sriamornsak, Thirawong, & Korkerd, 2007; Veronovski et al., 2012). Importantly, the kinetics of drug release can be fine-tuned by altering the rate of swelling and erosion of the metal ion alginate matrix.

The erosion rate of alginate gels can be effectively tuned by the use of redox responsive crosslinking agents (Bawa, Pillay, Choonara, & du Toit, 2009; Li, Maciel, Rodrigues, Shi, & Tomas, 2015). It was shown that chemically crosslinked alginate hydrogels are sensitive for the reduction of the linking disulfide bonds. The degradation of the hydrogel is triggered by a reductive environment, which induces the release of the incorporated active agent (Li et al., 2015; Maciel et al., 2013). Another promising strategy to produce redox responsive hydrogels is to crosslink alginate chains by a redox active metal ion which radically changes its affinity towards alginate when its oxidation state changes. The most successful systems are based on the Fe(III)/Fe(II) pair. Iron (III) interacts strongly with alginate (Dong, Dong, Cao, Han, & Ding, 2011; Lee, Min, & Kim, 1996), while Fe(II) is not capable of crosslinking

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the chains in aqueous solution (Bruchet & Melman, 2015; M. Giammanco, Sosnofsky, & Ostrowski, 2015; Jin et al., 2012). Thus by the in situ reduction of Fe(III) to Fe(II), the degradation of the ionically crosslinked hydrogel is triggered and the active ingredient is released. Three different approaches are described in the literature to utilize the Fe(III)/Fe(II) system. The electrochemical approach is based on the deposition of Fe(III)-alginate hydrogel on the surface of an electrode, where an independent signal induces the electrochemical reduction of Fe(III) (Jin et al., 2012; Katz et al., 2015). The photochemical approach is based on the application of a photoactive reducing agent (e.g. lactic acid) which can reduce Fe(III) only under illumination (Bruchet, Mendelson, & Melman, 2013; Giammanco et al., 2015; Narayanan, Melman, Letourneau, Mendelson, & Melman, 2012). Finally, Fe(III)-alginate hydrogel degradation can be triggered by the addition of a strong reducing agent (e.g. ascorbic acid) under controlled conditions (Bruchet & Melman, 2015).

In this study we showed that the drug delivery properties of dry Fe (III)-alginate aerogels can be tuned by incorporating ascorbic acid into the formulations. Fe(III)-alginate aerogels were synthesized by the sol-gel method in the form of spherical particles (d = 3–5 mm) and loaded with the model drug ibuprofen in supercritical CO_2. Some of the ibuprofen impregnated Fe(III)-alginate aerogels were co-impregnated with ascorbic acid. Finally, in vitro dissolution experiments were performed to show that the rate of drug release is significantly faster in the case of the latter system, as ascorbic acid in situ reduces Fe(III) to Fe(II) upon hydration of the aerogels.

2. Experimental

2.1. Materials

Two different Na-alginates with high guluronic acid content (high G, HG) and low guluronic acid content (low G, LG) from FMC Biopolymer (Norway) were used. Their detailed characterization is given elsewhere (Agulhon, Robitzer, Habas, & Quignard, 2014). The G/M ratio is 30/70 in the low G alginate and that is 70/30 in the high G alginate. $FeCl_3 \times 6H_2O$, ibuprofen [2-(4-(2-methyl-propyl)phenyl) propionic acid] and ascorbic acid were purchased from Sigma-Aldrich. Supercritical CO_2 was produced from 99.95% pure gas (AGA Gas GmbH, Germany). All aqueous solutions were prepared with Milli-Q water (Millipore). Other chemicals (HCl, NaOH, and NaH_2PO_4) were ACS reagent grade (Sigma-Aldrich).

2.2. Synthesis of Fe(III)-alginate aerogel beads

Spherical alginate beads (3.0–4.5 mm) were synthesized using the following method (Veronovski et al., 2013). The 2 w/w% aqueous solution of either the low G or the high G alginate was dropped into 0.05 M $FeCl_3$ solution (gelation bath) from fixed height of 10 cm. The $FeCl_3$ solution was slightly acidified previously with HCl to avoid the hydrolysis of Fe^{3+}. In order to achieve the homogeneous size distribution of the alginate droplets the alginate solutions were extruded through a plastic tube of d = 2 mm. Another batch of droplets was produced from both alginates implementing a needle at the end of the tube to obtain smaller gel spheres. During the preparation a moderate stirring (ca. 200 rpm) of the gelation bath was used to ensure the formation of spherical beads and to prevent the agglomeration and sedimentation of the droplets. After gelation, the beads were placed into a fresh 0.05 M $FeCl_3$ solution for 24 h. This was followed by multiple step solvent exchange. The alginate beads were placed for 24 h into 30 V/V %, 60 V/V%, 90 V/V% ethanol-water mixtures and two times into pure ethanol. After the last step, the ethanol content of the soaking liquid was checked by measuring its density with a density meter (DMA 4500, Anton Paar Company, Austria). The drying procedure was initiated only when the ethanol content reached min. 98.5 V/V% to ensure single phase conditions during subsequent supercritical drying (Subrahmanyam et al., 2015). The samples were dried with supercritical CO_2 at 45 °C and 140 bar using a continuous flow process in a high pressure autoclave, as described elsewhere (Goncalves et al., 2016; Smirnova, Mamic, & Arlt, 2003). Altogether, four different aerogel samples were produced as summarized in Table 1.

Table 1
Properties of the different Fe(III)-alginate aerogel samples (S = small, B = big). S_{BET} denotes the specific surface area determined by N_2 adsorption-desorption porosimetry. The error bars were calculated from parallel measurements (n = 3, for porosimetry n = 2).

Sample	G content (w/w%)[a]	Fe(III) content (w/w%)	bead diameter (mm)	S_{BET} (m^2/g)	Total pore volume (cm^3/g)
S-LG	30	8.56 ± 0.04	3.0 ± 0.2	420 ± 19	1.2 ± 0.2
B-LG	30	8.08 ± 0.03	4.5 ± 0.3	406 ± 18	1.8 ± 0.2
S-HG	70	6.99 ± 0.05	3.3 ± 0.2	442 ± 25	1.8 ± 0.2
B-HG	70	6.82 ± 0.02	4.5 ± 0.3	316 ± 19	1.2 ± 0.2

[a] Data taken from ref. (Agulhon et al., 2014).

Low-temperature supercritical drying in CO_2 was found to be optimal method for the production of dry, crack-free Fe(III)-alginate aerogel particles that retain the structure of the parent hydrogels (De Cicco et al., 2016; Tkalec et al., 2016; Zhao, Malfait, Guerrero Alburquerque, Koebel, & Nystrom, 2018). No other drying method ensures the good mechanical properties of the product accompanied by a high porosity and a dominantly mesoporous, interconnected pore network.

The Fe-content of the alginate samples was measured by the following method. The aerogel was dissolved in a 0.1 M EDTA solution at neutral pH. Water was evaporated and the dry, solid residue was digested with concentrated HNO_3. The Fe-content of this solution was measured by ICP-AES (Agilent Technologies ICP-OES SVDV 5100) after dilution.

2.3. Impregnation of Fe(III)-alginate aerogels

In the case of aerogels, the most efficient loading process developed for the encapsulation of nonpolar drugs is the adsorptive deposition of the drug from supercritical CO_2. This process is analogous to the traditional impregnation from organic solvents. Importantly, the porous matrix remains intact upon the removal of sc. CO_2 after impregnation, because no capillary stress forces are present in the system. This technique results in reasonably high loadings and often leads to the amorphization of the drugs inside the pores of the carrier (Gurikov & Smirnova, 2018). This technique is regarded to be optimal only if the aerogel is saturated with the drug in supercritical CO_2, thus the active ingredient is often used in excess.

In one set of experiments the Fe(III)-alginate aerogel beads were impregnated with ibuprofen alone, in another set of experiments the beads were simultaneously impregnated with ibuprofen and ascorbic acid. Weighted amounts of aerogel beads and active ingredients were wrapped separately in filter paper and placed into a 250 mL autoclave. Ibuprofen and ascorbic acid were taken in excess to guarantee the highest possible loadings at the experimental conditions, i.e. the concentrations of the components in sc. CO_2 were at their solubility limits. The vessel was warmed up to 45 °C and sc. CO_2 was pumped into it until the pressure reached 200 bar. These conditions were kept constant for 6 h. The pressure was released in two steps. First, a 120 bar pressure drop was carried out in 10 s, and from there the pressure was released at ca. 3–4 bar/min. After the depressurization the loaded aerogel samples were removed from the vessel.

The amount of the adsorbed ibuprofen and ascorbic acid were determined by UV–vis spectrophotometry after soaking the loaded aerogel samples in methanol. Ibuprofen was measured at 220 nm and ascorbic acid at 245 nm. Iron(III) salts do not dissolve in methanol and thus did