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Synthesis of polymer nanogels by electro-Fenton process: investigation of the effect of main operation parameters

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ABSTRACT

Recently, electro-Fenton (EF) process has been shown as a promising, facile, effective, low cost and environmentally-friendly alternative for synthesizing polymer nanogels suitable as biocompatible nanocarriers for emerging biomedical applications. Here, the electrochemically-assisted modification of poly(vinylpyrrolidone) (PVP) by EF process was studied to assess the role of key operation parameters for a precise modulation of polymer crosslinking and its functionalization with —COOH and succinimide groups. The dimensions of the nanogels, in terms of hydrodynamic radius (R_h) and weight-average molecular weight (M_w), can be tuned up by controlling the electrolysis time, current density (j) and PVP and Fe^{2+} concentrations, as demonstrated via dynamic and static light scattering and gel permeation chromatography analysis. Using PVP at 0.25 wt.%, Fe^{2+} at 0.5-1.0 mmol dm^{-3} and low j, short treatment times induced intramolecular crosslinking with chain scission, allowing size reduction of PVP particles from 24 to 9–10 nm. Longer reaction times and higher PVP and Fe^{2+} contents favored intermolecular crosslinking ending in M_w values higher than the initial 3.95×10^5 g mol^{-1}. An excessive $^{\bullet}OH$ dose from a too high circulated charge (Q), i.e., too prolonged electrolysis time even at low j or too high j even for short time, promoted intramolecular crosslinking ($R_h \sim 10$–12 nm) along with a very significant chain scission probably owing to the loss of mobility of the three-dimensional nanogel network. In conclusion, EF allowed transforming the architecture of linear, inert PVP chains into a functionalized nanogel with —COOH and succinimide groups that have great potential for further conjugation.

1. Introduction

Nanogels are crosslinked polymer particles of nanoscale size (typically < 200 nm), which can be considered similar to hydrogels when they are composed of hydrophilic polymer chains [1,2]. Since the first appearance of this family of nanoscale materials, their application as biocompatible carriers for a large plethora of biomedical and biotechnological applications has been explored [3–5]. In particular, these soft materials have gained growing interest for drug delivery because of their high loading capacity and stability [6–10], showing also potential use as pH and temperature sensors [11,12]. They are also employed as in vivo imaging tracers [13], in water treatment [14] and catalysis [15], as smart gating membranes for the fabrication of active photonic crystals and coatings, and for generating bioactive scaffolds in regenerative medicine [16].

The classical method for nanogels manufacture is chemical crosslinking [17,18]. It involves the formation of covalent bonds between the polymer chains during polymerization of monomers with di- or multifunctional co-monomers (crosslinkers), or self-assembly processes that exploit various interactions of a pre-formed polymer [19]. Conventional and novel polymerization techniques allow the preparation of nanogels with different architectures including core–shell and hollow nanogel particles. Click chemistry, amide crosslinking, and photo-induced crosslinking are suitable synthetic approaches starting from polymer precursors [20], although an accurate control of the experimental

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parameters is crucial for fine tuning of final particle dimensions. In general, particle size must be limited to tens or few hundred nanometers, with a narrow particle size distribution [19].

A more recent synthesis approach makes recourse to pulse radiolysis of semi-dilute polymer aqueous solutions, relying on a high energy input to yield free hydroxyl radicals homogenously in the solution bulk from water lysis, which in turn allow the formation of radicals onto the preformed polymer chains via H-abstraction [21]. The intra/intermolecular recombination of active centers fosters polymer crosslinking. This is then a fast, clean route to prepare high purity nanogels with controlled particle size [19,22,23]. Effective crosslinking of poly(vinylpyrrolidone) (PVP) [22–26], PVP copolymers [9,27,28] and other polymers [29] has been reported. As a major inconvenient, high energy radiation processes are not easily implementable into existing production lines, which limits their large-scale applicability.

Lately, the performance of alternative $^{\bullet}$OH-based methods requiring much simpler setups has been investigated. For example, the crosslinking of various preformed polymers like PVP and polyethyleneimine in water has been carried out by H_2O and H_2O_2 photolysis using UVC radiation [30,31]. In order to avoid the need of the expensive UVC lamps, some authors have performed crosslinking via chemical Fenton [32] and photo-Fenton [33] processes, whose efficacy is based on the occurrence of Fenton's reaction between added H_2O_2 and Fe^{2+} at optimal pH 2.8:

$$H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^- \qquad (1)$$

Fenton's approach is a hot topic nowadays, as demonstrated by its large impact in multiple domains. Its largest field of application is environmental chemistry, due to the great ability of $^{\bullet}$OH to inactivate microorganisms and degrade organic contaminants in water [34,35]. Fenton-based $^{\bullet}$OH has also been used to activate methane bond scission to form methanol for energy conversion [36]. In medicine, Fenton's free radicals trigger the lipid peroxidation, with a negative impact in cells and organs, being also detrimental for the digestion of proteins [37,38]. Conversely, $^{\bullet}$OH can act as a therapeutic agent to remove malignant tumors [39]. Regarding the synthesis of new materials, Fenton's reaction has been useful to apply Zn-doped carbon dots as biosensors with enhanced fluorescence [40] as well as to accelerate the crystallization of hydrothermal zeolite [41].

Worth mentioning, in addition to $^{\bullet}$OH (E^0 ($^{\bullet}OH/H_2O$) = 2.80 V|SHE) other radicals like $HO_2^{\bullet}$ (E^0 ($HO_2^{\bullet}/H_2O$) = 1.65 V|SHE) and $O_2^{\bullet-}$ (E^0 ($O_2^{\bullet-}/H_2O_2$) = 0.91 V|SHE) [29,37] formed in concomitant reactions due to the presence of the Fe^{3+}/Fe^{2+} couple, organic matter (R, $R^{\bullet}$) and, potentially, O_2, may have a role in the process. A very remarkable feature of Fenton and photo-Fenton processes is the occurrence of Fe^{2+} regeneration upon reduction of Fe^{3+} via chemical reaction with $HO_2^{\bullet}$, $R^{\bullet}$ and/or $O_2^{\bullet-}$, thus being constant the production of $^{\bullet}$OH. However, the need of high concentrations of Fe^{2+} salts (up to 10 mmol dm^{-3}) constitutes a major drawback due to the complex product purification necessary to reduce the residual concentration to the low values required by biomedical specifications.

In this context, the electrochemical technology may expand the applicability of classical Fenton systems. The electro-Fenton (EF) process is one of the most widespread electrochemical advanced oxidation processes (EAOPs), especially in the field of water treatment [42,43]. In EF, the electrolytic cell is composed of a low or high oxidation power anode connected to a carbonaceous air-diffusion cathode with large ability to generate H_2O_2 on site as follows:

$$O_{2(g)} + 2\,H^+ + 2\,e^- \rightarrow H_2O_2 \qquad (2)$$

Such in situ production is a very positive feature compared to classical Fenton, since it avoids the costs and risks from H_2O_2 synthesis, transportation, handling and storage. Note that H_2O_2 can be partly oxidized at the anode surface:

$$H_2O_2 \rightarrow HO_2^{\bullet} + H^+ + e^- \qquad (3)$$

A second, fundamental feature of EF is the need of much lower concentrations of iron ions (down to two orders of magnitude), which results from the continuous cathodic Fe^{2+} regeneration that sustains the catalytic process:

$$Fe^{3+} + e^- \rightarrow Fe^{2+} \qquad (4)$$

In a recent study, we investigated the PVP crosslinking activated by hydroxyl radicals electrogenerated through several approaches [44]. The interest of PVP as starting preformed polymer arises from its high versatility in biomedical applications. PVP shows high hydrophilicity and biocompatibility, absence of toxicity and ability to form interpolymer complexes [45]. It is used as plasma expander and additive in several pharmaceutical formulations. Emerging PVP-based materials include nanocarriers for gene therapy [46,47] or to enhance the delivery of biomolecules to the brain in the treatment of neurodegenerative diseases [8]. We provided the proof of concept that PVP crosslinking can be induced by an electrochemical process such as EF [44]. As a major feature, it is important to highlight that EF is a more accessible technology than radiation processing in terms of simplicity and safety, allowing an easy control of the various competing reactions upon accurate selection of experimental parameters.

The aim of this work is to carefully assess the role of key parameters that determine the electrochemically-induced transition from linear, water-soluble PVP to polymer nanogels by the formation of a crosslinked network under EF conditions. The effect of the electrolysis time, PVP and Fe^{2+} concentration, applied current and electric charge (Q) on the particle size and its polydispersity, molecular weight, functionalization and mineralization has been studied in detail using an undivided cell with an air-diffusion cathode and a dimensionally stable anode (DSA®). The extent of intra/intermolecular crosslinking depends on these factors, and their predominance is discussed along the paper. Note that, unlike usual work in other fields like environmental electrochemistry, where the highest production rate of $^{\bullet}$OH is preferred in order to have a very oxidizing environment, here it is critical to dose them adequately to prevent significant mineralization [48], and EF seems well-suited for this purpose.

2. Materials and methods

2.1. Chemicals

PVP k-60 ($M_n = 1.60 \times 10^5$ g mol^{-1}, $M_w = 3.95 \times 10^5$ g mol^{-1}, 45 wt.% solution) was purchased from Aldrich and used as received. PVP critical chain overlapping concentration in water (~1%) was determined by light scattering in a previous work [49]. Spectra/Por® cellullose acetate dialysis membranes of 12–14 kDa cutoff were purchased from Spectrum Laboratories, wheras 0.22 μm nylon and 1.22 μm cellulose acetate syringe filters were supplied by Aldrich. Oxygen (99.999% purity) and nitrogen (99.998% purity) were supplied by Air Liquide. Na_2SO_4 used as supporting electrolyte, H_2SO_4 added to work at pH 2.8, $FeSO_4$ employed as catalyst, KBr (FT-IR grade) needed for FT-IR analyses and NaN_3 for gel permeation chromatography (GPC) analyses were acquired from Sigma-Aldrich and Fluka. All solutions were prepared with double-distilled water.