Radiation Physics and Chemistry xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Radiation Physics and Chemistry

journal homepage: www.elsevier.com/locate/radphyschem

Preparation of nanogels by radiation-induced cross-linking of interpolymer complexes of poly (acrylic acid) with poly (vinyl pyrrolidone) in aqueous medium

Mohammadreza Ghaffarlou, S. Duygu Sütekin, Olgun Güven*

Department of Chemistry, Hacettepe University, 06800 Beytepe, Ankara, Turkey

ARTICLE INFO

Keywords:
Interpolymer complex
Nanogel
Radiation induced crosslinking
Poly(vinyl pyrrolidone)
Poly(acrylic acid)

ABSTRACT

Functional nanogels were prepared from interpolymer complexes (IPC) of poly (vinyl pyrrolidone) and poly (acrylic acid) by gamma irradiation of their aqueous solutions. The coil size of IPCs prepared under different experimental conditions (polymer molecular weight, concentration, mixing ratios, pH and temperature) were measured by Dynamic Light Scattering (DLS) technique prior to irradiation. At relatively low absorbed doses of 5 and 10 kGy, IPC nanogels with a range of 30–250 nm diameters, −12 to −28 mV zeta potentials and polydispersities lower than 0.17 were obtained. The sizes of the nanogels were found to be smaller than the size of the precursor IPC coil sizes (40–300 nm) due to the formation of intra-chain crosslinks. Thus a recipe of preparing multifunctional nanogels with double amphiphilic properties carrying polyacidic and nonionic polymer structures with the range of above listed properties has been developed. These nanogels show narrow size distribution and high colloidal stability increasing their potential to be used as biocompatible drug carriers with controlled-release properties. PVP-PAA IPC nanogels were characterized by dynamic light scattering (DLS), atomic force microscopy (AFM) and scanning electron microscopy (SEM) techniques.

1. Introduction

The design and synthesis of soft nanoparticles have been receiving considerable attention in biomedical applications. Polymeric nanogels which are nanosized hydrogel particles come into prominence especially in many biomedical applications like drug and vaccine delivery, biosensors, adsorbents, contrast agents, etc. due to their ability to trap biomolecules in a physical or chemical way (Chiellini et al., 2008; Tanner et al., 2011; Abd El-Rehim et al., 2013a; Guo et al., 2015; Asadian-Birjand et al., 2015; Behbahani et al., 2016; Yang et al., 2016). They assemble the beneficial features of hydrogels and nanomaterials such as high liquid uptake ability, high resistance to degradation, controllable chemical and physical structures together with tunable size in nanometer or micrometer scale, large surface area for bioconjugation, and high blood circulation times. Owing to these properties they can be used for encapsulation of biomolecules and may be actively or passively targeted to the required areas, e.g. tumor tissue. In every aspect nanogels are perfect candidates to be used in nanomedicine (Oh et al., 2008; Ryu et al., 2010; Asadian-Birjand et al., 2012; Sivaram et al., 2015; Molina et al., 2015).

The size and functionality of nanogels are two important properties to be controlled for specific drug delivery applications. Functionality can be introduced by chemical modification of already formed nanogels or by using polymers carrying specific functionalities. Functional groups are used to introduce stimuli-responsive properties to nanogels. These structures may respond to differences in pH, temperature, electromagnetic field, light, etc. which are highly important for controlled release of bioactive species at targeted sites (Goldberg et al., 2007; Kabanov and Vinogradov, 2009). Targeted drug delivery can be maintained by passive targeting which is size dependent or the enhanced permeability and retention (EPR) effect (Maeda et al., 2000; Maeda, 2010). In addition, pH or temperature responsive polymers may also manipulate drug or gene targeting in intra- or extracellular or tissue environment (Ganta et al., 2008; Lee et al., 2008; Zha et al., 2011).

Several methods were proposed for the preparation of nanogels e.g. inverse mini/micro emulsion, dispersion polymerization etc. (Oh et al., 2009; Delaittre et al., 2007; Sanson and Rieger, 2010). However, the use of monomers, organic solvents and surfactants make these procedures unfavorable regarding the potential applications of nanogels in biomedicine. Recently the use of interpolymer complexation via hydrogen bonding has emerged to evade the use of monomers where the complexation occurs between proton-donating poly (carboxylic acids) and proton-accepting non-ionic polymers (Khutoryanskiy,

* Corresponding author.

http://dx.doi.org/10.1016/j.radphyschem.2017.04.019
Received 30 October 2016; Received in revised form 15 March 2017; Accepted 29 April 2017

2007). However a proper control of parameters (molecular weight, pH, concentration and molar ratio) should be achieved in order to have a size control on precursor IPCs and resulting nanogels. Irradiation of IPCs by gamma rays promotes intramolecular crosslinking between complexed polymers and nanogels with permanent crosslinks can be obtained in an easy and effective way. The use of ionizing radiation makes nanogels free from additives, e.g initiators or crosslinkers rendering them non-toxic which is of primary importance for biomedical applications (Ulanski et al., 1998; Ulanski and Rosiak, 2004).

There are various examples of hydrogen-bonded interpolymer complexes (IPCs) with polymer components such as poly (methacrylic acid), poly(acrylic acid), poly(ethylene oxide), poly(vinyl pyrrolidone) (Khutoryanskiy et al., 2004; Li et al., 2010; Pinteala et al., 2005; Poe et al., 2004). These IPCs behave as novel individual compounds in aqueous media and their properties like pH or temperature sensitivity mostly differ from their constituents.

Complexation between PAA and PVP has been investigated thoroughly by different groups on the grounds that these IPCs combine the advantages of pH responsive PAA together with non-toxic PVP being both biocompatible (Park and Robinson, 1987; Lopes and Felisberti, 2003) and highly hydrophilic. Henke et al. presented an approach to synthesize PVP–PAA hydrogen-bonded nanogels by pulse radiolysis where they outlined the distinction between inter- or intra-molecular crosslinking and the requirements for nanogel formation (Henke et al., 2005). They also published a paper on PVP–PAA hydrogen-bonded complexes that clarify the aggregation and solvation phenomena of IPCs (Henke et al., 2011). Template polymerization of acrylic acid in an aqueous solution of PVP as a template polymer was also performed to synthesize PVP-g-PAA IPC structures (Chun et al., 2004; Rainaldi et al., 2000; Abd El-Rehim et al., 2007). Abd El-Rehim et al. (2013b) obtained PVP-g-PAA IPC nanogels with hydrodynamic mean diameters between 80 and 120 nm by gamma radiation-induced template polymerization of AA in the presence of PVP by controlling total absorbed dose, PVP molecular weight, pH and AA feed concentration. Grimaldi et al. (2014) used electron beam irradiation to synthesize PVP-g-PAA nanogels in size range of 14–26 nm using two different monomer concentrations of AA in the presence of linear PVP. Some recent studies on PVP/PAA nanogels and their use as drug-carrier systems support that PVP/PAA structure is advantageous due to its pH-responsive and biocompatible properties (Rashed et al., 2015; Picone et al., 2016).

In the first part of this work, we present a comprehensive approach on the factors affecting IPC formation between PVP and PAA with different molecular weights, concentrations and pH on the particle size of corresponding IPC structures. PVP and PAA based IPC nanogels were later synthesized by radiation induced intramolecular crosslinking of various IPCs via systematical parametric study.

2. Experimental section

2.1. Materials

Poly(vinyl pyrrolidone) (BASF, Mw = 360,000 and 1,300,000 g/mol), K10 M_w = 10,000 g/mol (Sigma-Aldrich), Poly(acrylic acid) (Aldrich, Mw = 250,000 g/mol) and poly(acrylic acid sodium salt) (PAANa) (Aldrich, Mw = 8000 g/mol) were used as received without further purification. The solvents, HCl, Acetone, and Tetrahydrofuran (THF) were supplied from Sigma-Aldrich and are of HPLC grade. Deionized water with 0.055 μS conductivity was used in all experiments. PAA (Mw = 8000 g/mol) was obtained from PAANa salt by the following procedure: 5 g PAANa was dissolved in 20 mL water acidified to pH 0.5 by addition of HCl. THF was added and the acidic solution was stirred for 12 h. Precipitated NaCl was removed by filtration and the polymer was left to dry at room temperature.

pH 211 Microprocessor pH-meter instrument was used at 25 ± 1 °C. The calibration was performed with pH 4.0, pH 7.0 and pH 10.0 buffer solutions prior to measurements. Conductivity measurements were carried out with Hanna MC226 conductivity meter at 25 °C.

2.2. Preparation of PVP-PAA interpolymer complex nanogels

Dilute aqueous solutions of PAA and PVP were prepared in water/acetone binary solvents (25% acetone by volume) with different molecular weight and concentrations. Acetone is used to suppress aggregation of water soluble polymers in dilute solutions (Details to be published). The coil sizes of polymers in these solutions were determined by using dynamic light scattering technique (DLS). Furthermore these polymer solutions were mixed to prepare stable PVP/PAA hydrogen bonded interpolymer complexes. Their size, size distribution and stability were followed by DLS. In the next step of the study these IPC solutions were irradiated to 5 and 10 kGy doses by using Nordion ^{60}Co gamma source with 0.022 kGy/h dose rate. The solutions were saturated with N_2O gas for 5 min prior to irradiation.

2.3. Dynamic Light Scattering (DLS)

In order to determine the hydrodynamic sizes of PVP, PAA, IPC coils and IPC nanogels in aqueous solutions Zetasizer Nano ZS (Malvern Instruments Ltd., UK) was used. The particle size was expressed by Z-Average which is an Intensity-based calculated value. Polydispersity Index (PdI) values were also determined to evaluate the particle size distribution.

Zeta potential measurements were performed by the combination of laser Doppler velocimetry and Phase Analysis Light Scattering (PALS). Neat polymer solutions (PAA and PVP), IPCs and IPC nanogels were measured at different pH and temperatures. Each solution was measured at least twice in capillary cells and each measurement was averaged from 3 runs.

2.4. Atomic Force Miscroscopy (AFM)

20 μL of IPC or IPC nanogel solutions were cast on a mica surface and dried at room temperature. Different regions of the samples were scanned with Veeco Multimode™ V scanning probe microscope (Veeco Metrology LLC, Santa Barbara, CA) with Nanoscope® IV controller. The measurements were performed at room temperature and in tapping mode with 1–10 Ω-cm phosphorus (n) doped Si tips (Veeco, MPP-11100-140) having f_0 values between 70 and 92 kHz.

2.5. Scanning Electron Microscopy (SEM)

The nanogel solutions were cast on silicone surface and the samples were sputter-coated before imaging using a precision etching coating system (PECS, 682, Gatan Inc, Pleasanton, CA) with 10 nm thick gold/palladium. The size and shape of the nanogels were observed using a scanning electron microscope (ESEM, FEI Quanta 200 FEG, FEI Company). The analyses were made in high vacuum and relatively at low acceleration voltages (5 kV) using back-scattered electron technique.

3. Results and discussion

3.1. Formation of PAA and PVP interpolymer complex

It is well known that secondary interactions between polymers may end up with interpolymer complex formation in aqueous solutions. One of the frequently observed types of macromolecular complexation is by hydrogen bonding where the complexation occurs between a proton donor (generally a polyacid) and a proton acceptor polymer. A stable IPC formation occurs at a certain pH range which depends on the dissociation degree of polyacid (Khutoryanskiy, 2007). PVP is able to form strong H-bonding with PAA compared to other well-known H-bond acceptor polymers such as poly(ethylene oxide) or poly(vinyl