Synthesis of Polymeric Nanogel via Irradiation of Inverse Micelles Technique

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ABSTRACT

Covalently cross-linked nanogels were prepared via irradiation of inverse micelles that had been prepared from radiation crosslinkable polymer, water, oil and surfactant. A mixture of polymer, water, heptane and sodium dioctyl sulfosuccinate (AOT) at certain compositions forms inverse micelles with the size ranging from 2 to 8 nm. The hydrophilic head of the surfactant facilitates encapsulation of water soluble polymer. If the entrapped polymer is radiation crosslinkable, it is expected that upon irradiation, polymerization shall take place in such small and confined space, leading to formation of nano-sized polymeric gel. Meanwhile, emulsion at 2 nm size was chosen for gamma irradiation process. The formation of the nano-sized discreet gel using irradiation of inverse micelles technique was proven at a dose as low as 5 kGy to obtain nanogel sized ~ 95 nm.

Keywords: Polymer, nanogel, radiation

INTRODUCTION

Nanogel refers to gel that is less than 100 nm size. It is a well known fact that in this size range, almost all materials will have several advantages that are not seen in their macro form. In this case, among the advantages are large surface areas for better attachment of ligand and prolong stability in the blood stream. These advantages are useful, especially that this gel is used in the treatment of diseases which need a constant drug concentration in the blood (Hashida *et al.*, 1996).

The methods used to synthesize such materials can be categorized into two. The first is the classical chemistry routes (McAllister *et al.*, 2002; Oh *et al.*, 2008; Vinagradov *et al.*, 2002) and the radiation route (Ulanski *et*

al., 1999). The classical chemistry route is normally multi-steps and it involves prohibitive and harmful toxin substances which are used as initiators, additives and crosslinking agents. The radiation route, on the other hand, offers a simpler, more efficient and cleaner process (Rosiak *et al., 2002*).

When an aqueous medium is irradiated with an ionizing radiation, absorption of the energy from the irradiation source will occur, and this will then lead to the formation of hydroxyl radicals, hydrogen atoms and solvated electrons in the medium. Out of the three species, hydroxyl radical is known to be responsible for abstracting hydrogen atom from macromolecules (Alexander *et al.,* 1957). This species may react with crosslinkable polymeric macromolecules to create active sites. When two or more of these macromolecules with active sites are in close proximity, the combination may take place and thus form 3D covalent links between the chains (known as the intermolecular crosslinking). This will finally lead to wall-to-wall gelation (macrogel). If the combination process proceeds in a confined space such as in a micelle, discreet gel is expected to form. Polymerization in such a confined space will result in the formation of single gel particle, and normally, the size of the gel formed has a dependency on the size of the micelle used. In this work, the use of inverse micelles from AOT was demonstrated as nanoreactor to produce polyethylene glycol diacrylate (PEGDA) nanogel.

MATERIALS AND METHODS

Materials

PEGDA, with an average molecular weight of around 700, AOT and n-heptane (99.5%) were purchased from Sigma Aldrich. PEGDA, AOT and n-heptane were used without further purification. Ultrapure water was used throughout the research.

Ternary Diagram

Inverse micelles were formed by adding AOT into a series of PEGDA and n-heptane mixture until clear micro emulsions were formed. Suitable conditions for microemulsions formation were identified through systematic mapping of ternary phase diagrams. The ternary phase diagram of the PEGDA in n heptane microemulsion system is shown in Fig.1. The area which is covered by the black dotted lines represents the single-phase transparent microemulsion. In this work, the formulations are taken from the lower right part of the ternary diagram, where it is hypothetically known to yield clear single-phase inverse micelles that are smaller than 100 nm (Calvo *et al.,* 1997).

Preparation of Emulsion

Emulsions were prepared by dissolution of PEGDA in ultrapure water, stirring and filtering it with 0.45 μm (Minisart, Sartorius). After that, 10 ml of PEGDA was added into 100ml of n-heptane containing 0.05 to 0.25 of AOT. The size of emulsion formed was measured using dynamic light scattering and the smallest size of emulsion was found to be 2 nm, and the emulsion of this particular size was chosen for electron beam irradiation process.
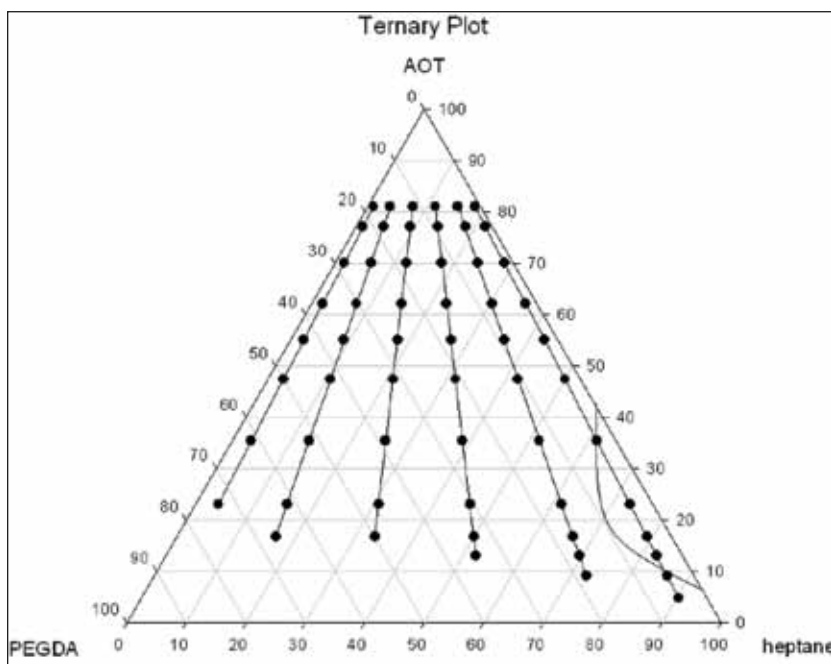
Fig.1: Ternary plot diagram PEGDA/AOT/n-heptane with the hypothetical single phase region containing W/O micelles represented by the curve

Preparation of Nanoparticle

The PEGDA solution (10%) was prepared by dissolving the polymer in ultrapure water by stirring overnight at room temperature. 10 ml of the PEGDA solution was added into 100 ml of n-heptane containing 0.15 M of AOT. The mixture was then irradiated at 1, 3, 5, 10, 15, 20 and 30 kGy with 3 MeV of voltage and 5 mA of beam current. All the mixtures were saturated with argon gas prior to the irradiation. The nanogel formed during the irradiation process was then recovered by evaporating n-heptane using a rotary evaporator and precipitating the dry mass with an acetone methanol (9:1) solution. The precipitate was then washed 5 times with the acetone alcohol solution to remove the excess of AOT. After the washing process, the precipitate was solubilised in ultrapure water, followed by dialysis using 12 kD cut off dialysis membrane (Spectrum) and was finally lyophilized.

Dynamic Light Scattering Studies

Dynamic light scattering (DLS) studies were done using DLS spectrometer of Nanophox from Sympatec GmbH (Germany) with a 10 mWatt HeNe laser beam at a wavelength of 632.8 nm at 90° scattering angle at room temperature. Prior to the measurement, the lyophilized nanogel was resolubilized in ultrapure water and filtered with 0.22 μm pore size filter (millipore). The 3D cross correlation of the function of the scattering intensity was analyzed using a cumulant analysis to obtain the hydrodynamic diameter, D_h, and the dispersity information for the particles.

RESULTS AND DISCUSSION

AOT is a surfactant with hydrophilic head with two hydrocarbon tails (*see* Fig.2a) and simplified in this article as in Fig.2b for ease of depiction. It has been reported elsewhere that dissolution of AOT, at a critical micellar concentration in non-polar solvent such as n-heptane, forms a thermodynamically stable inverse microemulsion (Ming *et al.,* 1998). In water-oil mixture, the hydrophilic heads of the surfactant are oriented inward, thus entrapping aqueous cores, whereas the non-polar groups or the tails are extended outwards into the hydrophobic phase. This condition makes each microemulsion a suitable template for polymerization of water soluble crosslinkable polymer such as PEGDA (Fig.3a). Microemulsion with a narrow size distribution in the range of 2 nm was observed by DLS upon addition of 10% PEGDA into 0.15 M AOT in n-heptane. By decreasing the amount of AOT for the same system, a larger size of microemulsion was observed. This particular trend is consistent with the data obtained for acrylamide in the AOT system (Candau *et al.,* 1984; Shervani *et al.,* 2000). The size increase of the microemulsion was observed with an increase in the amount of AOT. Upon irradiation on such ternary system, energy imparted will be absorbed by the oil phase producing excess of electron, which will be scavenged by the micelles in the system producing solvated electron, e^-_{aq} (Joshi *et al.,* 2003; Gebicki *et al.,* 2000) and hydroxyl radical by direct radiolysis of the water core surrounded by AOT (Joshi *et al.,* 2003). The unstable hydroxyl radical will react with the entrapped PEGDA to form macroradicals through hydrogen abstraction (Fig.3b). The macroradicals will then undergo combination (Fig.3c) within the micro emulsion forming nanogel (Fig.3d). It was observed that the size of the nanogel increased with the increasing dose (*see* Table 1). This could be due to the diffusion of micelles that leads to a combination of macroradicals from different micelles during longer irradiation period for higher doses.

Table 1: The effect of irradiation dose on the particle size

Dose (kGy)	Size (nm) ± error (nm)
0	0
1	0
3	0
5	95.8 ± 1.3
10	276.8±60.5
15	368.7±50.6
20	409.1±47.6
30	461.4±54.9

CONCLUSIONS

Polymeric nanogel can be synthesized via irradiation of inverse micelles. The inverse micelles with size of 2 nm can be used to entrap radiation crosslinkable polymer. The formation of the nanosized discreet gel has proven that inverse micelles can be utilized as a nanosized reactor in synthesizing covalently cross-linked nanosized gel.
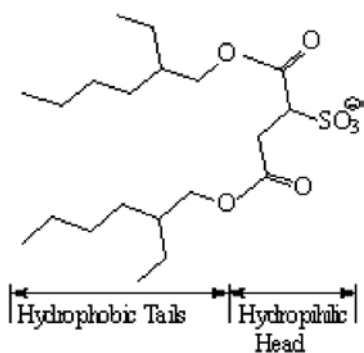
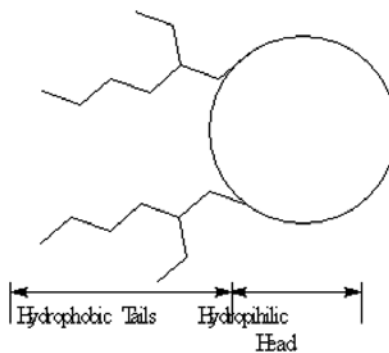Fig.2(a): Molecular structure of AOT

Fig.2(b): A simplified molecular structure for AOT with hydrophilic head and hydrocarbon tails
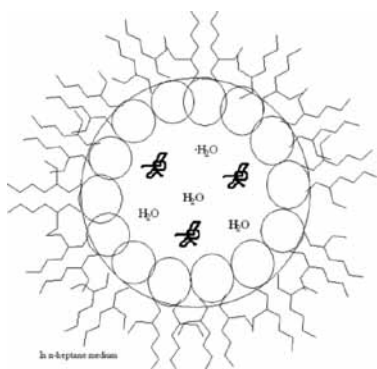

Fig.3(a): Microemulsions formed above critical micelle concentration, with the heads of the surfactant oriented inwards to the water phase and the tails are extended outwards into the oil phase.
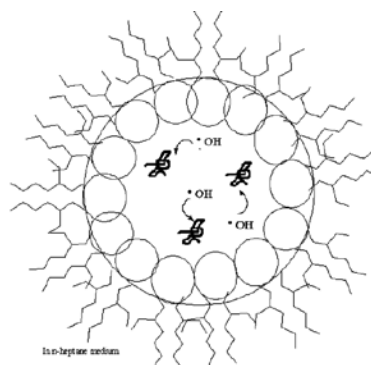

Fig.3(b): The PEGDA polymerization initiation in the micelle by hydroxyl radicals produced by irradiation.
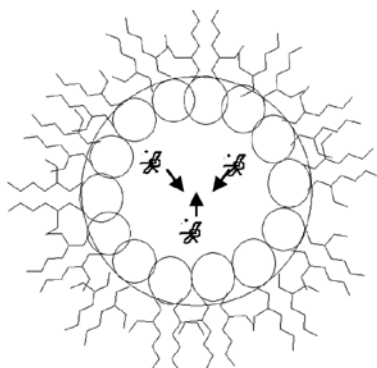

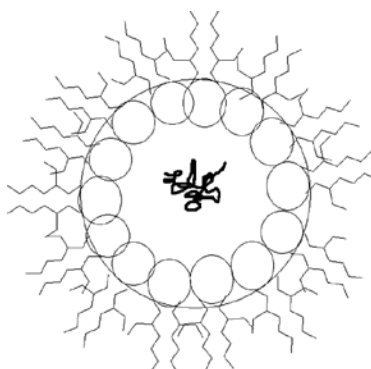Fig.3(c): The PEGDA macroradicals combination to produce polymer networks.

Fig.3(d): Nanogel particle produced

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