

Dendrimer Graft Hyperbranched Hydrogels

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Abstract

A novel dendrimer graft hyperbranched hydrogel was developed as a potential candidate for the biomedical applications. This hydrogel was composed of a first generation aliphatic polyester dendrimer and the DTPA (diethylenetriaminepentaacetic acid) moieties. This hydrogel showed a few very unique properties compared to the linear cross-link hydrogels. The hydrogel aggregated to give very uniform size in the acidic and neutral conditions. The average diameter of the particle size is about 15 μm , whereas in the basic conditions, the particle size of this hydrogel deaggregated to 400 nm without any treatment after four days. SEM results suggested that this is the result of a dimer product.

Keywords: Dendrimer, Hyperbranch, Hydrogel

Introduction

In general hydrogels are insoluble, cross-linked polymer network structures with hydrophilic homo- or hetero-copolymers, which can absorb significant amount of water within its polymeric framework. Hydrogel has long been known for its biomedical applications, such as in the delivery of the therapeutic or diagnostic drugs, in the tissue engineering, in the cell culture, in the bioseparations and the biosensors. Several excellent review articles in this field had been published [1-3]. Dendritic polymer is highly branched three-dimensional macromolecules with rather rigid structure. Compared to the traditional linear polymers, dendrimer has controlled structure with globular shape in one molecular weight via precise controlled reaction sequences, moreover on the periphery there are many reactive chain ends. Because of its high value in nature, most of the applications on dendrimers are directed toward the biomedicines, such as MRI contrast agent, gene delivery vessel and small molecule drug carrier. Recent reviews are given [4-5].

In this work, we have synthesized a class of novel dendrimer graft hyperbranch hydrogels, which is composed of a first generation aliphatic polyester dendrimer and the DTPA (diethylenetriaminepentaacetic acid) moieties. As a potential material for the biomedical applications in nanometer scale, we have done some preliminary studies on its particle behavior at various pH values. The results were further confirmed by the scanning electron microscopy (SEM).

Experiment

General considerations: all chemicals were purchased commercially. The first generation dendrimers were synthesized, according to the Fréchet's publications [6]. The preparation of the DTPA-dianhydride was followed by the literature method with slight modification [7]. The DSC trace was recorded by the TA Instruments Universal V3.5B, with two cycles from room temperature to 250 °C, at temperature increment 10 °C/min.. The ^1H NMR spectra are given by the Bruker AC-200 NMR spectrometer with 10% NaOD/D₂O solution in δ ppm. The particle size distribution was analyzed by the Beckman Coulter LS Particle Size Analyzer, with Fraunhofer optical model in water solution.

General procedure for the synthesis of hydrogels: The mixture of one molar equivalent of the first generation aliphatic polyester dendrimer and three molar equivalents of DTPA-dianhydride were together dissolved in the solvent mixture of dimethylsulfoxide/pyridine. The reaction mixture was stirred in the room temperature over night, a slightly gray look gel was formed in the wall of reaction vessel. Followed by the addition of water 10-mL, the reaction mixture was further stirred for five hours. The organic solvents were decanted first and the gel was dissolved in the 1 N aqueous solution, followed by the addition of methanol. A black precipitate was removed by simple filtration. The solvents of the solution were removed and the resulting white powder product was dried in vacuum. The yields of the reaction in general were quantitative.

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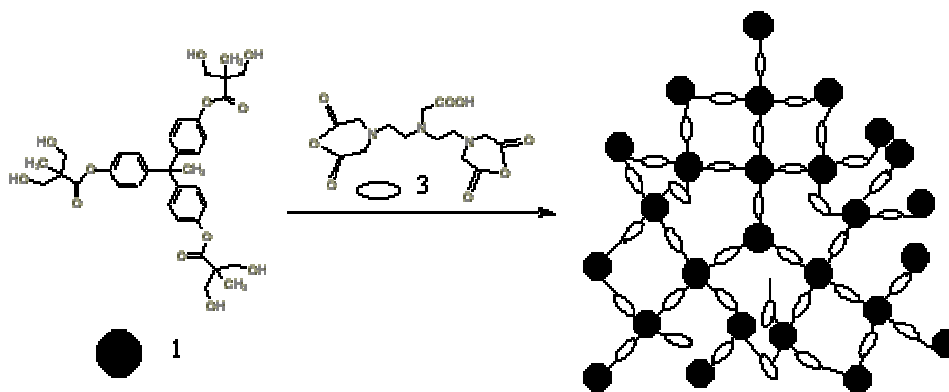


Figure 1. A cartoon drawing for the structure of the hydrogel

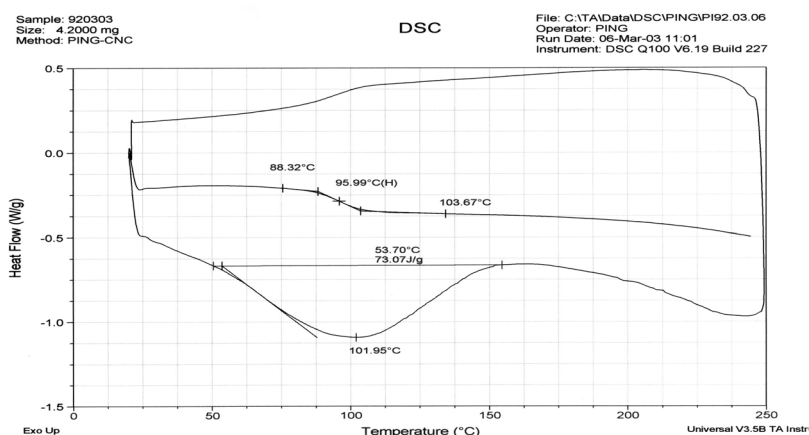
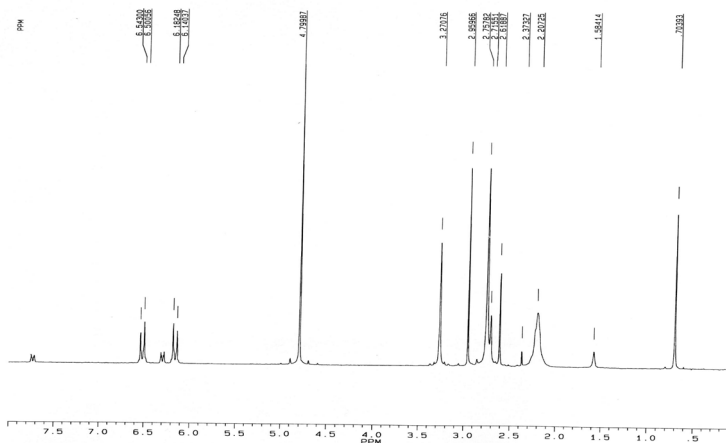


Figure 2. The DSC trace of the hydrogel

Figure 3. The ¹H NMR spectrum of the hydrogel

Results and Discussion

Synthesis and characterization of hyperbranch hydrogel: A hydrogel was formed when three molar equivalents of the DTPA-dianhydride was reacted with one molar equivalent of the first generation aliphatic polyester dendrimer. The reaction result in cartoon drawing is shown in the Figure 1. The hydrogel was first characterized by the DSC and the trace was shown in the figure 2.

The DSC experiment was performed in two cycles. For the first cycle, a broad endothermic trace with peak temperature at ca. 102 °C was seen, which indicated significant amount of water still remained in the hydrogel even the sample was pre-dry in the oven at 80 °C for four hours. The second temperature increment of the trace shows a clear T_g point at the 96 °C, which confirmed the product's polymer in nature.

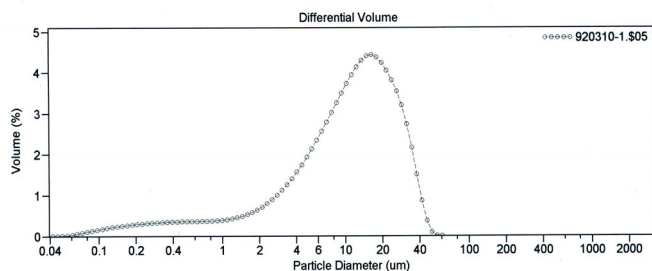


Figure 4. The particle size distribution of hydrogel in PH 10

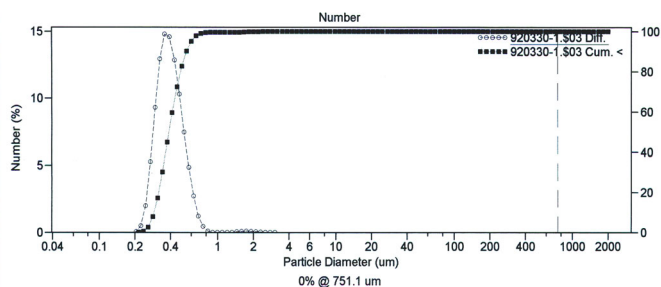


Figure 5. The particle size distribution of hydrogel in pH 10 after four days

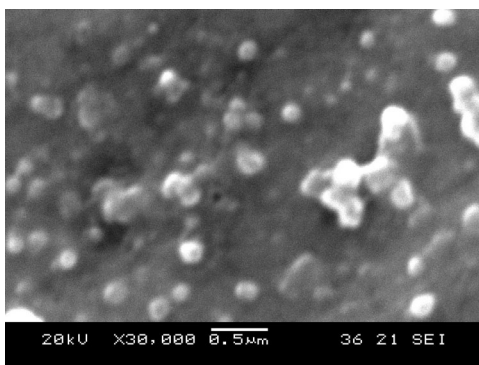


Figure 6. SEM picture of the hyperbranch hydrogel

The structure of the product was further characterized by the 200 MHz ^1H NMR spectrometer in 10 % NaOD/D₂O solution. The spectrum is shown in the figure 3.

The ^1H NMR spectrum of the hydrogel shows rather sharp resonance peak, indicating that the structure of this hydrogel is rather well defined compared to the traditional random cross-linked hydrogel. The spectrum showed both the DTPA-ester and the first generation aliphatic polyester dendrimer moieties resonance peaks, indicating the formation of the hydrogel. However, the very weak doublet resonance peaks at δ 6.3 and 7.7 ppm seemingly suggest that under the reaction condition some aliphatic polyester dendrimers are decomposed in the gel network. Interesting to note that under the basic condition the hydrogel was deaggregated in the aqueous solution, forming rather uniform size nanoparticles

(see below for the detail discussion). Thus we tentatively propose the structure of this hydrogel is hyperbranched in spherical shape, instead of highly cross-linked hydrogels in bulk.

Particles size distribution studies: The particle size of the resulting hydrogel was analyzed by the light scattering particle size analyzer in the aqueous solution. The average particle size of the hydrogel is measured after ultrasound irradiation at various pH values buffers. The samples were prepared in 1%-measured solution. Generally speaking the hydrogels are in rather mono distribution with mean particle size of 15 μm at pH 4, 7 and 10 buffer solutions (see figure 4). The particle size distribution is rather stable at pH 4 and 7 buffer solution. However in the case of pH 10, the particles deaggregates significantly even without ultrasound irradiation. After four days, the particle size was reduced to 400 nm, without any further deaggregation observed (figure 5). Although there are many $-\text{COOH}$ group present in this hydrogel, the PH dependent swelling effect of this hydrogel is not observed in this study, this may be due to the relatively short polymer chain of the hyperbranch hydrogel.

The SEM studies: The samples were prepared by dissolving the hydrogel solid in 1 N NaOH solution. This solution was transferred to the sample tray and the solvent was removed in vacuum. The sample was then sputtered with gold before observations. Figure 6 is the observation results. The observed particle size is about 200 nm in rather uniform size. This result seeming suggested that under basic condition, the particle size of this hyperbranch hydrogel is likely to be 200 nm and the result obtained from the particle distribution studies in PH 10 solution is the dimeric particle.

Reference

- [1] Galaev, I.Y. and Mattiasson, B., "Smart' polymers and what they could do in biotechnology and medicine", *Trend in Biotechnology*, 17: 335-340, 1999.
- [2] Galaev, I.Y., Gupta, M.N. and Mattiasson, B., "Use Smart Polymers for Bioseparations", *CHEMTECH*, 12, 19-25 1996.
- [3] Qiu, Y. and Park, K., "Environment-sensitive hydrogels for drug delivery", *Advanced Drug Delivery Review*, 53: 321-339, 2001.
- [4] Krause W., Hackmann-Schlichter N., Maier F.K. and Muller R., "Dendrimers in diagnostics", *Dendrimers II: Top. Curr. Chem.*, 210: 261-308, 2000.
- [5] Hecht S., Frechet J. M. J., "Dendritic Encapsulation of Function: Applying Nature's Site Isolation Principle from Biomimetics to Materials Science", *Angew. Chem. Int. Ed. Engl.*, 40: 74-91, 2001.
- [6] Ihre H., Padilla De Jesús O. L. and Fréchet J.M.J., "Fast and convenient divergent synthesis of aliphatic ester dendrimers by anhydride coupling", *J. Am. Chem. Soc.*, 123: 5908-5917, 2001.
- [7] Hnatowich D.J. et al., "The preparation and labeling of DTPA-coupled albumin", *Int. J. Appl. Radiat. Isot.*, 33: 327-332, 1982.

含樹狀高分子之高分枝水膠

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摘 要

我們發展出一種新型含樹狀高分子而且呈高分枝狀結構的水膠系統。這水膠的組成是由一個第一代的烷基聚酯樹狀高分子與二乙基三胺五醋酸(DTPA, Diethylene triaminepentaacetic acid)所組成的。這水膠系統在酸性和中性的環境下會凝成具有規則大小約 $15 \mu\text{m}$ 的微粒。然而在鹼性的環境中，微粒之粒徑則分散至約 400 nm ，從電子顯微鏡下觀察得知，此為兩顆微粒凝聚之結果。

關鍵詞： 樹狀高分子、高分枝、水膠

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