Synthesis and characterization of aromatic polyether dendrimer/ poly(2-hydroxyethyl methacrylate) copolymer as nano drug carriers

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Abstract

Highly branched, functionalized polymers have potential to act as efficient drug carrier system. The aromatic polyether dendrimers are spherical, highly ordered, multibranched, nanometer-sized macromolecules having positively charged ether groups on the suface at physiological conditions. In this study, we synthesized a kind of dendrimer/poly (2-hydroxyethyl methacrylate) nanocomposite for oral drug delivery. The aromatic polyether dendrimer (generation 2, hyperbranched polyether with $-CH_2OH$ functionality, 3,5-Dihydroxybenzoic acid core) was prepared from generation 2, hyperbranched polyether dendrimer with $-COOCH_3$ form in excellent yield. FTIR, NMR and DSC studied suggest that monomer predominantly forms a complex with polyether dendrimers because of the ionic interaction between the $-CH_2OH$ end groups of dendrimer and the -OH group of 2-hydroxyethyl methacrylate monomer. [Life Science Journal. 2008; 5(3): 35 – 40] (ISSN: 1097 – 8135).

Keywords: poly(2-hydroxyethyl methacrylate); polyetheric dendrimer; nanocomposite; carrier system

1 Introduction

The most important characteristic of any drug is efficacy. This characteristic may often reduced because of the inability to deliver the drug to the specific cells or tissues[1,2]. After administration, the drug may pass through different physiologic barriers and/or pathways, decreasing the actual amount of drug that reaches the site. In the search for an ideal carrier system, the dendrimers may have significant potential. Dendrimers are synthetic macromolecules with a well-defined globular structure[3]. The need for advanced materials with improved and new properties for a variety of technological applications has created a demand for both new forms of matter and for polymers that have highly controlled molecular architectures[4,5]. The established approach to dendritic macromolecules has traditionally involved a divergent process in which growth is started from a polyfunctional core and continued outwards in a stepwise manner that affords larger and larger macromolecules as the process is continued[6]. The fundamental attribute of the convergent approach is that it begins at what will be the periphery of the molecule, proceeding inwards[7]. It is this feature more than any other that allows for unparalled control over molecular architecture[8]. Figures 1 and 2 show the structure of the generation 1 and 2 hyperbranched aromatic polyether dendrimer[9,10].

We investigate the potential of dendrimers amd hyperbranched polymers as drug carrier system using poly(2-hydroxyethyl methacrylate), since the methodologies for evaluation of the cellular activity of dendrimer are well known[11,12]. In this paper, we explore the interaction of the poly(2-hydroxyethyl methacrylate), with aromatic polyetheric dendrimer. The nature of the interaction was characterized by FT-IR and ^{1}H-NMR spectroscopy. Figures 3 and 4 show schematic synthesis method of polyether dendrimer-poly(2-hydroxyethyl methacrylate) conjugate[13,14].

2 Subjects and Methods

All reactions were performed under an atmosphere pressure. All reagents and solvents, unless otherwise specified, were obtained from Merck Chemical Co. Melting points were obtained on a Mel-Temp melting point
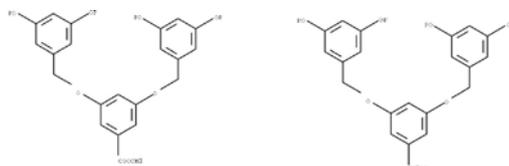
[*]Corresponding author. Email: saboktakin123@yahoo.com

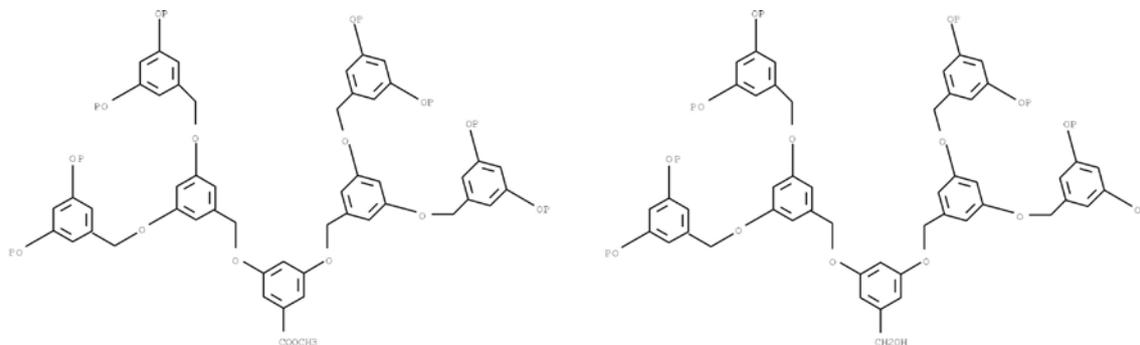**Figure 1.** Aromatic polyether dendrimers structure (1st generation)

Figure 2. Aromatic polyether dendrimer structures (2nd generation)
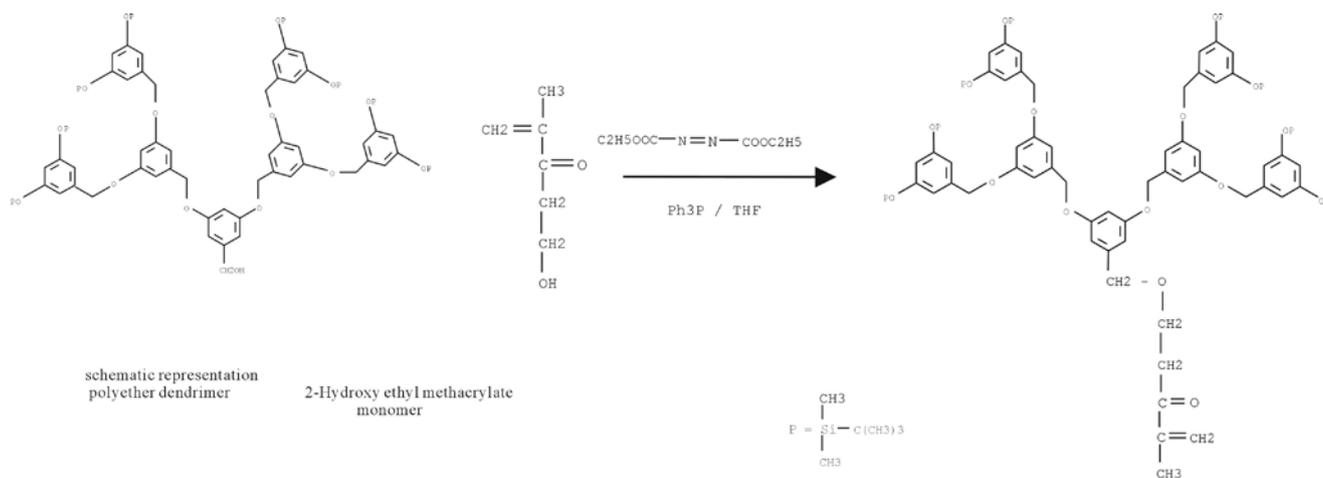

Figure 3. Schematic synthesis of 2-hydroxyethyl methacrylate conjugated with polyether dendrimer

apparatus. G2 polyether dendrimer and 2-hydroxyethyl methacrylate were obtained from Aldrich chemical company. ¹H-NMR spectrum were recorded on a 400 MHz spectrometer. But were referenced to tetramethylsilane. Analytical TLCs were run on commericial Merck plates coated with silica gel GF250 (0.25 mm thick). Fourier transfer infrared (FTIR, Bruker) spectroscopy was used to identified the polymer surface. Specta were obtained in the wave number range of 400 – 4000 cm⁻¹. Spectra of samples were recorded from KBr in 1 : 10 (wt/wt) ratio.

2.1 Preparation of 3,5-bis(3,5-bis(3,5-bis(t-butyldimethylsilyloxy) benzyloxy)benzyloxy)benzyl alcohol

A mixture of the G2-COOCH₃ dendrimer (AB8, hep-

tamer) (0.8 g, 0.285 mmol) in dry THF (100 ml) and dropwise to a suspension of LiAlH4 (2.5 g, 60 ml) in dry THF (50 ml). After reflux for 1 hour, the solution was treated with aqueous NaOH (1 M, 15 ml), filtered and evaporated. The residue was chromatographed on silica gel with dichloromethane as the eluent to give the heptameric alcohol as a colorless glass (0.768 g, 96%). R_f = 0.91, ψ_{max} (KBr)/cm 3053, 2960, 2932, 2860, 1544; δ_H (CDCl₃) 0.1 (s, 48H, CH₃), 0.9 (s, 72H, t-Bu), 1.60 (t, 1H, OH), 4.62 (d, 2H, CH₂OH), 4.68 (s, 8H, CH₂O-), 4.88 (s, 4 H, CH₂O-), 6.14 (t, 4H, J2, 4H 3rd gen. Ar), 6.21 (t, 2H, J2, 2/4-H 2nd gen. Ar), 6.41 (d, 8H, J2, 2/6-H 3nd gen. Ar), 6.41 (d, 4H, J2, 2/6H 2nd gen. Ar). Found: C, 76.4%; H, 6.8%, C₁₇₇H₁₈₈O₁₅Si₈.
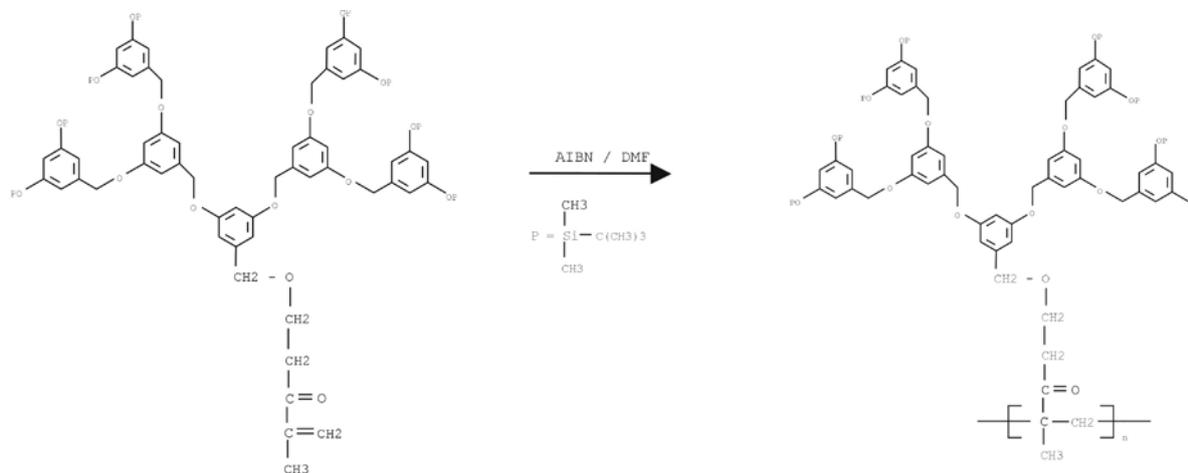
Figure 4. Schematic synthesis of 2-hydroxyethyl methacrylate / polyether dendrimer copolyme

2.2 Preparation of 3,5-bis(3,5-bis(3,5-bis(t-butyldimethylsilyloxy) benzyloxy)benzyloxy)benzyl alcohol dendrimer and 2-hydroxyethyl methacrylate conjugate

A mixture of the G2-CH$_2$OH dendrimer (AB8, heptamer) (0.17 g, 0.279 mmol), 2-hydroxyethyl methacrylate (0.176 g, 0.127 mmol), diethyl azo dicarboxylate (0.05 g, 0.317 mmol) triphenyl phosphine (0.083 g, 0.317 mmol) was dissolved in dry THF. The reaction mixture was stirred for 24 hours in the dark, then evaporated using rotaevaporator to remove methanol. The traces were dried under vacuum in order to remove methanol completely. To these traces, deionized water was added. Residue was chromatographed on silica gel with dichloromethane- petroleum ether (3 : 1) as the eluent to give the pure conjugate. The 2-hydroxyethyl methacrylate-dendrimer conjugate obtained was in the form of a yellow powder (R$_f$ = 0.92, 68.1%).

2.3 Preparation of 3,5-bis(3,5-bis(3,5-bis(t-butyldimethylsilyloxy)benzyloxy)benzyloxy)benzyl alcohol dendrimer and 2-hydroxyethyl methacrylate copolymer

A mixture of the 2-hydroxyethyl methacrylate -G2-CH$_2$OH dendrimer (AB8, heptamer) conjugate (4.83 g, 0.37 mmol), azo bis isobutyronitryle (AIBN) (61 mg, 0.37 mmol), DMF (10 ml) at 61 – 62 ℃ was stirred for 24 hours. The mixture was then filtered through PTFE membrane (Millix Millipore) of pore size 200 nm, and then lypophilized to remove water. After approximately 180 minutes, the sample were sprayed into a liquid nitrogen bath cooled down to 77 ℃, resulting in frozen droplets. These frozen droplets were then put into the chamber of the freeze-dryer. In the freeze-drying process, the products were dried by a sublimation of the water component in an iced solution. The 2-hydroxyethyl methacrylate-

dendrimer copolymer obtained was in the form of a white powder (m.p. 253 – 254 ℃, 73.0%).

3 Results and Discussion

Figure 5 shows the FT-IR spectrum of the G2-COOCH$_3$ dendrimer (AB8, heptamer) where the % of transmittance is plotted as a function of wave number (cm^{-1}). The characteristic FT-IR peaks at 3078, 3053, 2961, 1718 cm^{-1} are due to the presence of =CH bond stretching vibrations, the aliphatic CH bond in protect groups (t-butyldimethylsilyloxy) and carbonyl (C=O) group, respectively.

Figure 6 shows the FT-IR spectrum of the G2-CH$_2$OH dendrimer (AB8, heptamer). The characteristic FT-IR peaks at 3408, 2960, 2932, 2860, 1544 cm^{-1} are due to the presence of OH phenolic group , the aliphatic and aromatic =CH bond in protected methyl groups and C=C bond of aromatic group, respectively.
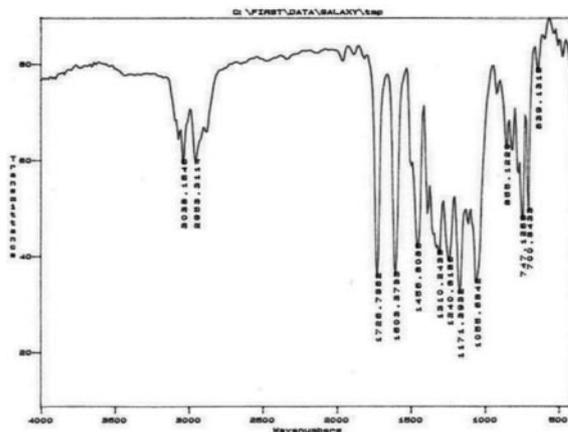

Figure 5. FT-IR spectrum of [G2]-COOCH$_3$ dendrimer
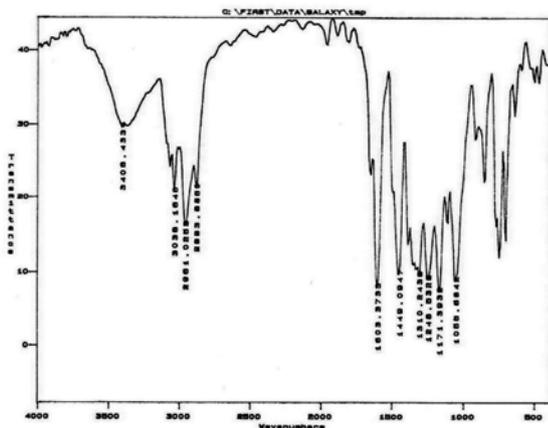
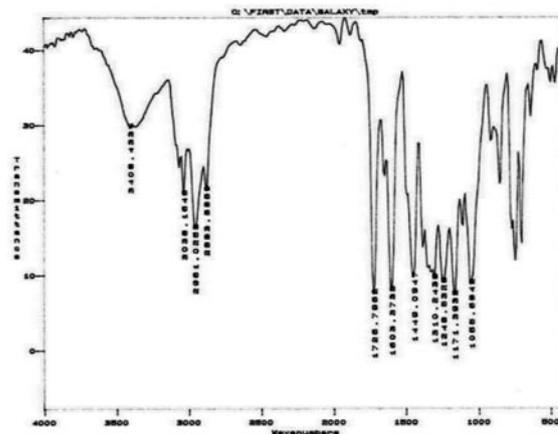**Figure 6.** FT-IR spectrum of [G2]-CH$_2$OH dendrimer

Figure 7. FT-IR spectrum of [G2]-CH$_2$OH dendrimer/poly(2-hydroxyethyl methacrylate) copolymer
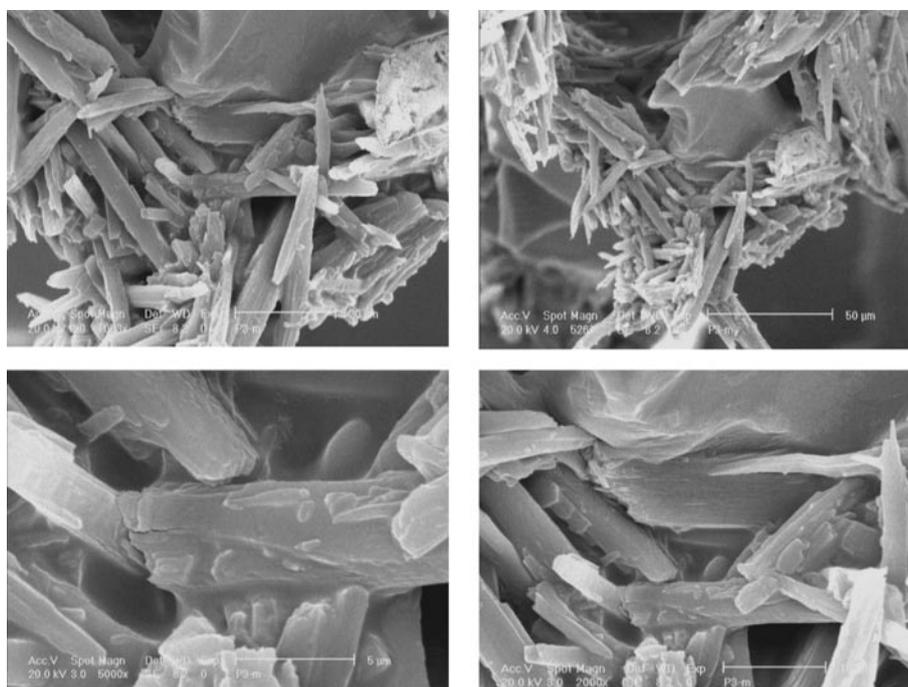

Figure 8. SEM of [G2]-CH$_2$OH Dendrimer/2-hydroxyethyl methacrylate copolymer

Also, Figure 7 shows the FT-IR spectrum of the G2-CH$_2$OH dendrimer (AB8, heptamer)/poly(2-hydroxyethyl methacrylate) nanocomposite. The characteristic FT-IR peaks at 3408, 2960, 2932, 2860, 1544, 1726 cm^{-1} are due to the presence of OH phenolic group, the aliphatic and aromatic =CH bond in protected methyl groups and C=C bond of aromatic group and carbonyl (C=O) group of 2-hydroxyethyl methacrylate, respectively.

Figure 8 shows the scanning electron micrography (SEM) of aromatic polyether dendrimer/poly(2-hydroxyethyl methacrylate) copolymer that synthesized by chemical reaction. This copolymer is very sensitive to the temperature that due to the intractionelectron and sample. SEM images were obtains from a diluted solution of the copolymer particle. The white spots are poly(2-hydroxyethyl methacrylate) nano particles. The SEM image shows the presence of poly(2-hydroxyethyl methacrylate) spherical particles in polyfunctional dendrimeric matrix, which are homogenenously distributed throughout the copolymers, which is also confirmed from ^{1}H-NMR studies[15].

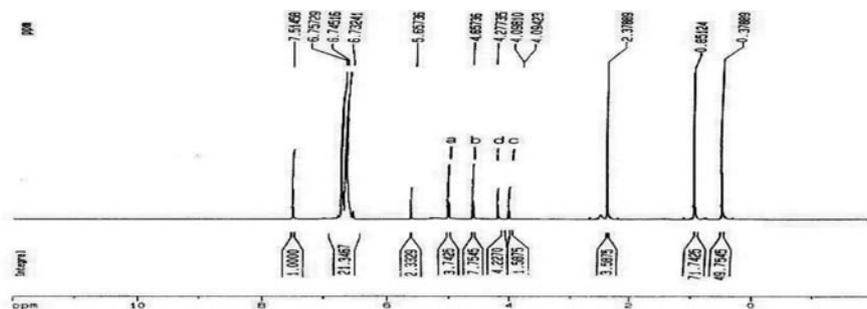The ability of the dendrimer to form a complex with

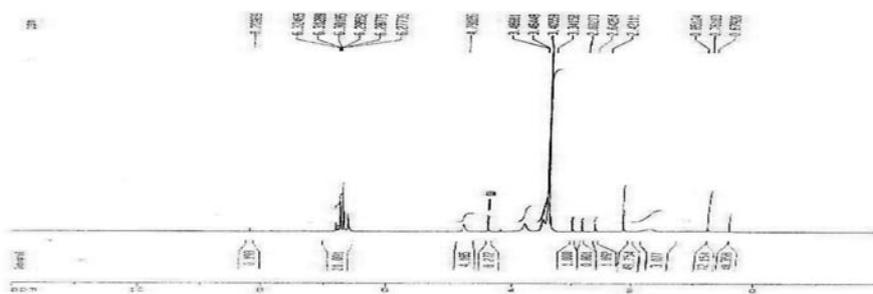**Figure 9.** 400 MHz 1H-NMR spectrum of [G2]-CH$_2$OH dendrimer/2-hydroxyethyl methacrylate conjugate (CDCl$_3$)

Figure 10. 400 MHz ^{1}H-NMR spectrum of [G2]-CH$_2$OH dendrimer/poly(2-hydroxyethyl methacrylate) copolymer (DMSO-d$_6$)

2-hydroxyethyl methacrylate monomer depends on the core-suface groups of dendrimer, electrostatic interactions between the dendrimer and the monomer, and the ability of the drug to form a conjugate with the dendrimer through chemical bonding. Therefore, it is possible to manipulate the incorporation process for a given monomer by appropriate selection of the dendrimer and the surface functionality. One might expect that the 2-hydroxyethyl methacrylate with the carboxylic group may form a complex with surface OH groups of polyether dendrimer.

Figure 9 shows the 400 MHz ^{1}H-NMR spectrum of [G2]-CH$_2$OH dendrimer/2-hydroxyethyl methacrylate conjugate in which three regions can be seen. The silane group 48 and 72 protons are in the regions of 0.37 and 0.85 ppm, respectively. The resonance of CH$_2$ protons (c group), CH$_2$ 4 protons (d group), CH$_2$ 8 protons (Heptamer protons), benzylic protons of heptamer (a group), vinylic CH$_2$ protons are 4.09, 4.15, 4.27, 4.86, 5.66 ppm, respectively.

The resonances for the aromatic protons of the monomer units at dendrimer occur in the region 6.73 ppm separate resonances are observed in the appropriate ratio for each layer of monomer units. The solvent peak occur in the region 7.51 ppm.

Figure 10 shows the 400 MHz ^{1}H-NMR spectrum of [G2]-CH$_2$OH dendrimer/poly(2-hydroxyethyl methacrylate) nanocomposite in which three regions can be seen. The silane group 48 and 72 protons are in the regions of 0.10 and 0.85 ppm, respectively. The resonance of methyl group, polymer CH$_2$ protons, CH$_2$O protons, CH$_2$ 8 protons (Heptamer protons), CH$_2$ protons of heptamer (a group), are 1.68 , 2.27, 4.17, 4.65, 4.79 ppm, respectively. The resonances for the aromatic protons of the monomer units at dendrimer occur in the region 6.28 – 6.32 ppm separate resonances are observed in the appropriate ratio for each layer of monomer units. The DMSO peak occur in the region 3.34 – 3.48 ppm.

The thermal behavior of a polymer is important in rela-

tion to its properties for controlling the properties of co-polymer. The glass transition temperature (Tg) was determined from the DSC thermograms. The values are given in Table 1. The higher Tg values probably related to the nanocomposite size, which would decrease the flexibility of the chains and the ability of the chains to undergo segmental motion, which would increase the Tg values. On the other hand the introduction of a strongly phenolic OH group can increase the Tg value because of the formation of internal hydrogen bonds between the polymer chains.

Table 1. DSC data and composition of copolymer

Nanocomposite	Molar composition of mono-mers in the feed		Tg (ºC)
	Dendrimer (gr) / HEM*(gr)	AIBN (gr)	
1	4.83	0.06	126

*: 2-hydroxyethyl methacrylate

4 Conclusion

The ability of the dendrimer to form a copolymer with 2-hydroxyethyl methacrylate monomer was explored using aromatic polyether dendrimer as model base polymer. The nature of 2-hydroxyethyl methacrylate -dendrimer interaction were explored using FT-IR, ^{1}H-NMR and SEM. Our studies suggest that the aromatic polyether dendrimer may predominantly form a conjugate with the -OH group of 2-hydroxyethyl methacrylate. This nanocomposite is stable in deionized water and methanol and can be use as drug carrier system. Current studies are exploring the complexation/conjugation ability of these dendrimers to a wide variety of drugs carrier.

Acknowledgment

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