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Synthesis and characterization of multifunctional hyperbranched polyesters as prospective contrast agents for targeted MRI

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ABSTRACT

Based on a commercially available hyperbranched aliphatic polyester, novel multifunctional gadolinium complexes were prepared bearing protective PEG chains, a folate targeting ligand and EDTA or DTPA chelate moieties. Their relatively high water relaxivity values coupled with biodegradability of the hyperbranched scaffold, folate receptor specificity render these non-toxic dendritic polymers promising candidates for MRI applications.

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Low molecular weight contrast agents based on gadolinium chelates are widely used for enhancing the contrast in magnetic resonance imaging (MRI).[1–3] Gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA, Magnevist®) and Gadolinium-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (Gd-DOTA, Dotarem®) complexes as well as their derivatives are used in MRI for the diagnosis of a wide range of pathologies.[4] They are characterized by predominant positive signal enhancement in T_1-weighted MRI, tissue distribution and particularly high safety profile.[5,6] These complexes, however, exhibit rapid clearance rates from vascular circulation and fast renal excretion requiring, therefore, high dosage administration. Another shortcoming of these molecules is their non-specific tissue distribution. Due to these shortcomings, intense efforts are being made for developing target-specific agents coupled with high contrast efficiency.[7]

The conjugation of low molecular weight gadolinium chelates to macromolecules has been used to increase the rotational correlation time resulting in a relaxivity improvement per gadolinium atom.[6] Gd^{3+} complexes based on linear polymers,[8,9] dendrimers,[10–12] and hyperbranched polymers[12] have been developed in order to enhance sensitivity and decrease clearance rates. Specifically, dendrimers and hyperbranched polymers (collectively characterized as dendritic polymers) which are highly branched nano-sized macromolecules, consisting of a central core, branching units, and terminal groups can conveniently be functionalized with appropriate moieties affording a diversity of functional materials including MRI contrast agents,[11–13] drug,[14–16] and gene[17–19] delivery systems.

In this study, multifunctional dendritic polymers were synthesized and characterized bearing gadolinium chelates, a protective coating and a tissue-specific targeting moiety. Specifically, ethylenediaminetetracetic acid (EDTA) or diethylenetriaminepentaacetic acid (DTDA) groups, which can form gadolinium chelates,[20] were introduced on the surface of the hyperbranched polyester Boltorn™ H40 (BH40) which is biodegradable[21] and of low polydispersity after appropriate fractionation.[22] The introduction of poly(ethylene glycol) chains (PEG) at the external surface protects the synthesized contrast agents in the biological milieu, prolonging their circulation time, which is a property of critical importance for contrast agents.[8,23] Additionally, the introduction of a folate group at the end of PEG chain provides tissue specificity through receptor-mediated endocytosis.[24,25] PEGylated BH40 is known to be easily hydrolyzed in the presence of lipases (ca. 50% hydrolysis of ester bonds in 24 h),[21] while folate receptors are over-expressed in a wide variety of human cancers and on activated macrophages.[26] Water relaxation studies as well as cell toxicities were investigated in vitro using folate receptor positive (HeLa) and folate receptor negative (A549) tumor cell lines.

The functionalization of hyperbranched aliphatic polyester BH40 with EDTA or DTPA groups and poly(ethylene glycol) chains, with one of the latter chains bearing the folate targeting ligand at its end, that is, BH40-EDTA-PEG-Folate and BH40-DTPA-PEG-Folate was achieved employing the steps shown in Schemes 1–3. BH40 was initially interacted with EDTA or DTPA dianhydride in dry

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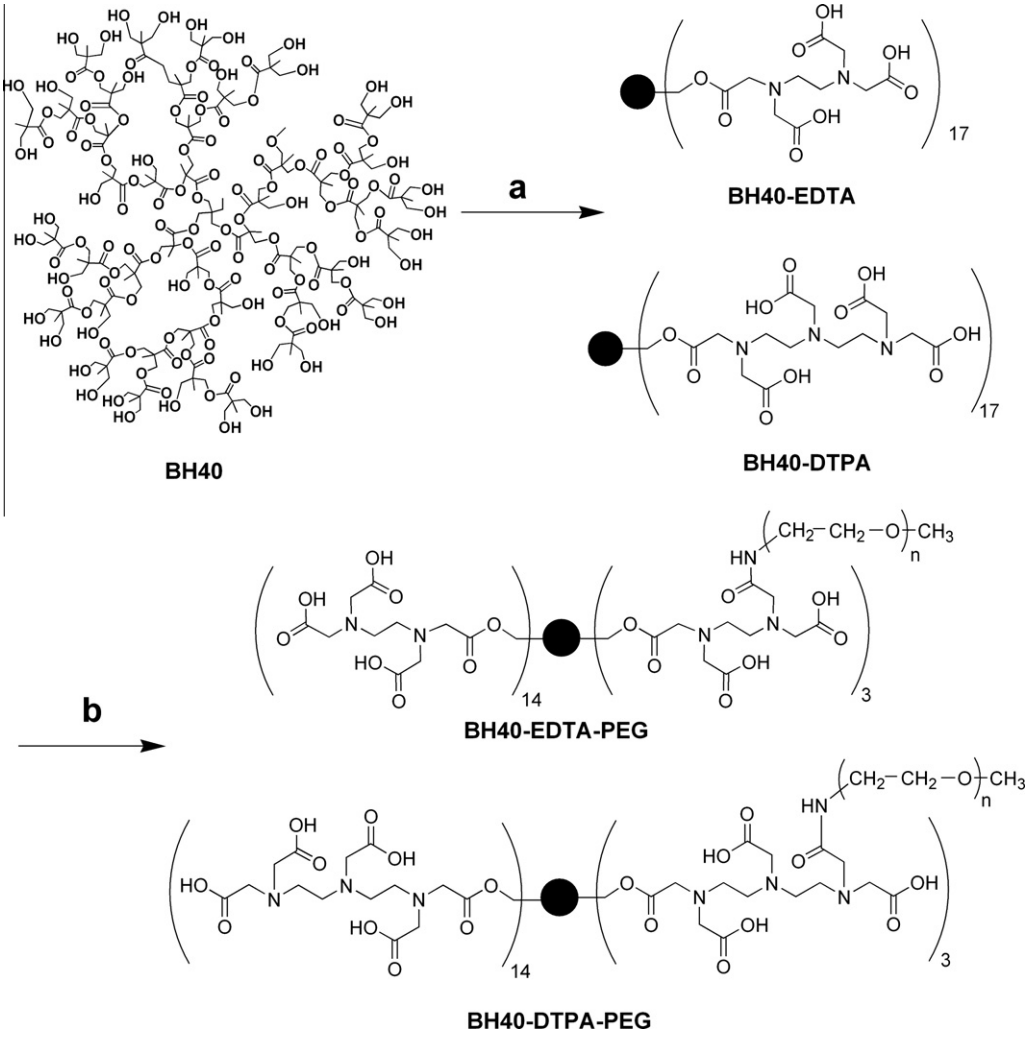
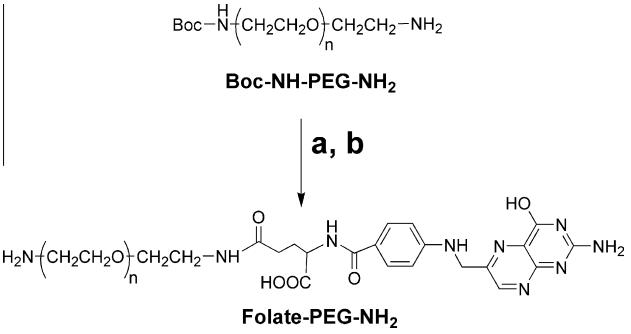


Scheme 1. Reagents and conditions: Synthesis of BH40-EDTA and BH40-EDTA: (a) EDTA or EDTA dianhydride (33 equiv), dry pyridine, 24 h, room temperature, 82% and 74% yield, respectively. Synthesis of BH40-EDTA-PEG and BH40-EDTA-PEG: (b) mPEG-NH_2 (3.3 equiv), EDC (3.3 equiv), NHS (3.3 equiv), 50 mM MES buffer, overnight, room temperature, 63% and 66% yield, respectively.



Scheme 2. Synthesis of Folate-PEG-NH_2. Reagents and conditions: (a) folic acid (1 equiv), DCC (1 equiv), NHS (1 equiv), triethylamine (1 equiv), dry DMSO, overnight, room temperature, addition of Boc-NH-PEG-NH_2 (0.25 equiv) in pyridine, overnight, room temperature, 82% yield; (b) deprotection/neutralization; i—TFA/$CHCl_3$, 3 h, room temperature; ii—$CHCl_3$, triethylamine, 2 h, room temperature, 96% yield.

pyridine at room temperature for 24 h (Scheme 1), affording the EDTA or DTPA polyester derivatives, BH40-EDTA or BH40-DTPA, respectively (82% and 74% yield). The average number of EDTA and DTPA moieties per polymer was 17, as revealed by ^{1}H NMR spectra (see Supplementary data). In the second step, PEG chains were introduced to these polyester derivatives by the reaction of methoxy poly(ethylene glycol)-amine with BH40-EDTA and BH40-DTPA (Scheme 1) affording the PEGylated derivatives, BH40-EDTA-PEG and BH40-DTPA-PEG, respectively (63% and 66% yield, respectively). This coupling reactions were performed using a 20% excess of both 1-ethyl-3(3-dimethyl aminopropyl)carbodiimide (EDC) and *N*-hydroxysuccinimide (NHS) in aqueous 50 mM 2-morpholinoethane sulfonic acid (MES) buffer (pH 5.5) at room temperature for 24 h.[27] The completion of the reaction was confirmed by the ninhydrin test and the final products were received after dialysis against water followed by lyophilization. The average number of attached PEG chains per polymer was found to be 3, as established by ^{1}H NMR spectra (see Supplementary data).

In the final step, the Folate-PEG-NH_2 intermediate was prepared by a method analogous to one previously reported (Scheme 2).[28] Briefly, folic acid was activated to its hydroxysuccinimidylester, using *N*-hydroxysuccinimide (NHS) and *N*-dicyclohexylcarbodiimide (DCC), and subsequently reacted with α-*tert*-butyloxycarbonylamino-ω-amino poly(ethylene glycol) (H_2N-PEG-NH-Boc), affording the amino protected Folate-PEG derivative in 82% yield. The cleavage of Boc group was achieved using TFA/$CHCl_3$ (1:1 v/v) to afford Folate-PEG-NH_2 in 96% yield. This compound was subsequently interacted with BH40-EDTA-PEG and BH40-DTPA-PEG

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