# Synthesis and characterization of aromatic polyether dendrimer / Mesalamine (5-ASA) nanocomposite as drug carrier system

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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 / Mesalamine [5-aminosalicylic acid (5-ASA)] 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 and NMR studied suggest that Mesalamine predominantly forms *a complex* with polyether dendrimers because of the ionic interaction between the –OH end groups and the carboxyl group of Mesalamine (Mesalamine contains both amine (basic) and carboxylic acid (acidic) functional groups). [The Journal Of American Science. 2007;3(4):45-51]. (ISSN: 1545-1003).

**Keywords:** Drug, Mesalamine, nanocomposite, dendrimer, nanocomposite, dendrimer, carrier system

## 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 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 1,2 show the structure of the generation 1 and 2 hyperbranched aromatic polyether dendrimer [9,10].

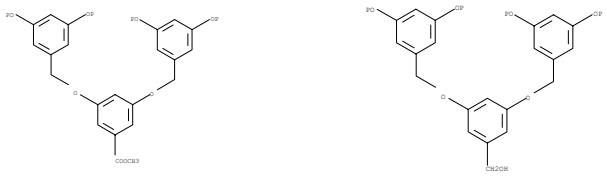


Figure 1. Aromatic polyether dendrimers structure (1 generation)

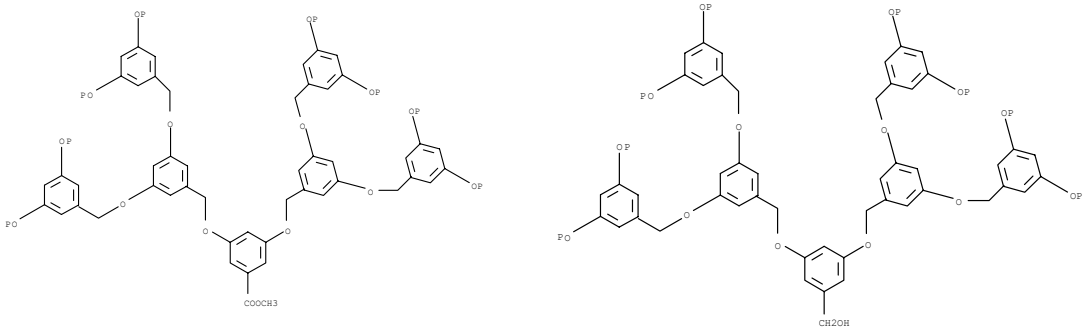



Figure 2. Aromatic polyether dendrimer structures (2 generation)

We investigate the potential of dendrimers and hyperbranched polymers as drug carriers using Mesalamine (5-aminosalicylic acid, 5-ASA) as a model drug, since the methodologies for evaluation of the cellular activity of Mesalamine are well known [11]. Mesalamine contains both amine (basic) and carboxylic acid (acidic) functional groups. Figure 3 shows structure of the Mesalamine [12,13]. In this paper, we explore the interaction of the drug with aromatic polyetheric dendrimer. The nature of the interaction was characterized by FT-IR and $^1$H-NMR spectroscopy. Figure 3 show schematic synthesis method of polyether dendrimer – mesalamine conjugate [14].

***Experimental***

***Materals***

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 apparatus. G2 polyether dendrimer and mesalamine (5-ASA) were obtained from Aldrich chemical company.$^1$H- 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.

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

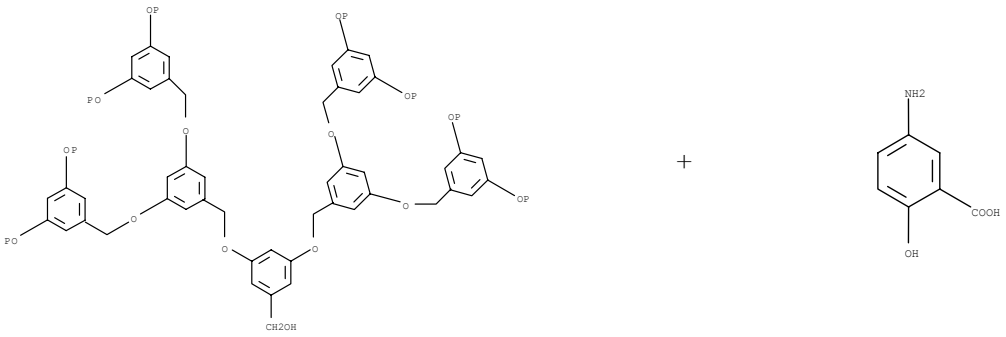
A mixture of the G2-$COOCH_3$ dendrimer (AB8, heptamer) (0.8 g, 0285 mmol) in dry THF (100 ml) and dropwise to a suspension of $LiAlH_4$ (2.5 g, 60 ml) in dry THF (50 ml). After reflux for 1 h, the solution was treated with aqueous NaOH (1 M, 15 ml), filtered and evaporated. The residue was chromatographed 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 , $\psi_{max}$(KBr)/cm$^{-1}$ 3053, 2960, 2932, 2860, 1544; $\delta_H$ (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, 4H, CH2O-), 6.14 (t, 4H, J2, 4H 3$^{nd}$ gen. Ar), 6.21 (t, 2H, J2, 2/4-H 2$^{nd}$ gen. Ar), 6.41 (d, 8H, J2, 2/6-H 3$^{nd}$ gen. Ar), 6.41 (d, 4H, J2, 2/6H 2$^{nd}$ gen. Ar).

Found: C, 76.4%; H, 6.8%, $C_{177}H_{188}O_{15}Si_8$)

- ** preparation of 3,5-bis(3,5-bis(3,5-bis(t-butyldimethylsilyloxy) benzyloxy)benzyloxy)benzyl alcohol dendrimer and 5-ASA conjugate.*

5-aminosalicylic acid (5-ASA) was dissolved in methanol following which the dendrimer was added .The reaction mixture was stirred for 24 h in the dark, then evaporated using rotaevaporator to emove methanol. The traces were dried under vacuum in order to remove methanol completely. To these traces, deionized water was added. This solution was stirred in the dark for 24 h. This was extracted the drug – dendrimer coplex, as dendrimer is soluble in water while 5-ASA is not. The solution was then filtered through PTFE membrane (Millix Millipore) of pore size 200 nm, and then lypophilized to remove water. After approximately 180 min, the sample was sprayed into a liquid nitrogen bath cooled down to 77° K, resulting in frozen droplets. These frozen droplets were then put into the chamber of the freeze-dryer. In the freeze-drying process, the products are dried by a sublimation of the water component in an iced solution. The drug – dendrimer complex obtained was in the form of a white powder.




*schematic representation polyether dendrimer* *Mesalamine (5-ASA)*

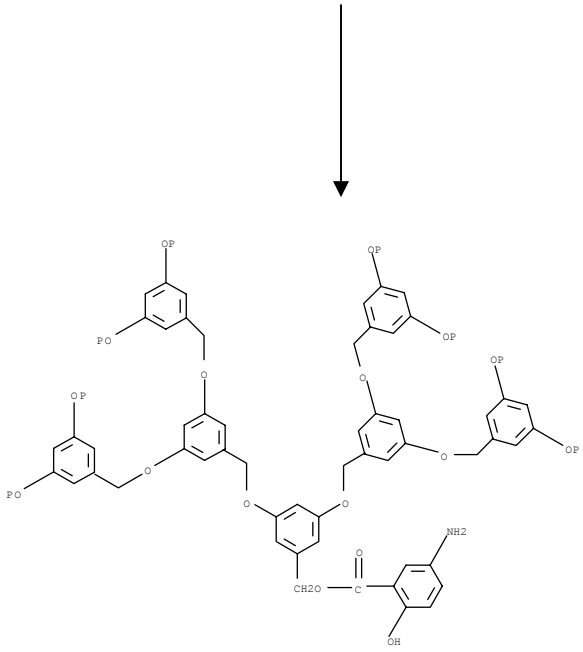



Figure 3. Sschematic synthesis method of mesalamine conjugated polyether dendrimer

***Results and discussion***

- ***Fourier transfer Infrared spectra***

Figure 1 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.

Also, Figure 2 shows the FT-IR spectrum of the G2-$CH_2OH$ 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.

- ***Scanning electron micrography***

Figure 3 shows the SEM of aromatic polyether dendrimer / Mesalamine (5-ASA) nanocomposite that synthesized by chemical reaction. This nanocomposite is very sensitive to the temperature that due to the intractionelectron and sample. Scanning electron micrography images were obtains from a diluted solution of the nanocomposite particle. The white spots are drug nano particles. The SEM image shows the presence of 5-ASA spherical particles in polyfunctional dendrimeric matrix, which are homogenenously distributed throughout the composites, which is also confirmed from $^1$H-NMR studies [15].

- ***$^1$H-NMR spectroscopy***

The ability of the dendrimer to form a complex with drugs depends on the core- suface groups of dendrimer, electrostatic interactions between the dendrimer and the drug, 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 drug by appropriate selection of the dendrimer and the surface functionality. One might expect that the mesalamine with the carboxylic group may form a complex with surface OH groups of polyether dendrimer.

Figure 4 shows the 400 MHz $^1$H-NMR spectrum of of [G2] – $CH_2OH$ Dendrimer/Mesalamine conjugate in which three regions can be seen.The resonances for the aromatic protons of the monomer units at dendrimer occur in the region 6.5-6.7 ppm separate resonances are observed in the appropriate ratio for each layer of monomer units ,and at highest field , resonances for the methylene protons occur in the region 4.90-5.00 ppm. The aromatic protons of 5-ASA are observed at 6.9 and 7.8-7.95 ppm, phenolic protons at 8.1 ppm, amidic protons at 8.9 ppm and acidic protons of 5-ASA at 9.3 ppm.

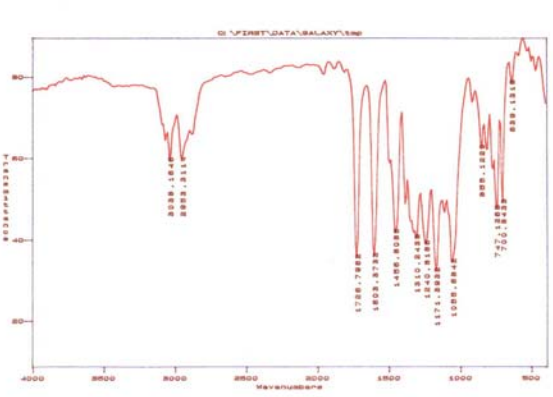


Figure 4. *FT-IR spectrum of [G2] –$COOCH_3$ Dendrimer*

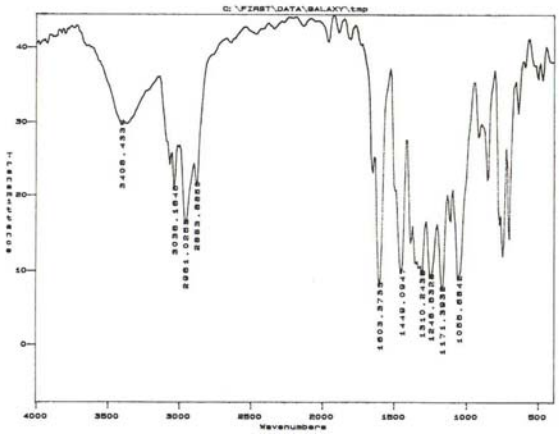



Figure 5. *FT-IR spectrum of [G2] – $CH_2OH$ Dendrimer*

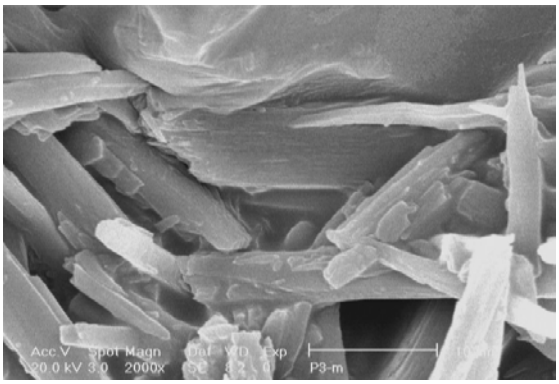



Figure 6. *SEM of [G2] – $CH_2OH$ Dendrimer/Mesalamine(5-ASA) conjugate*

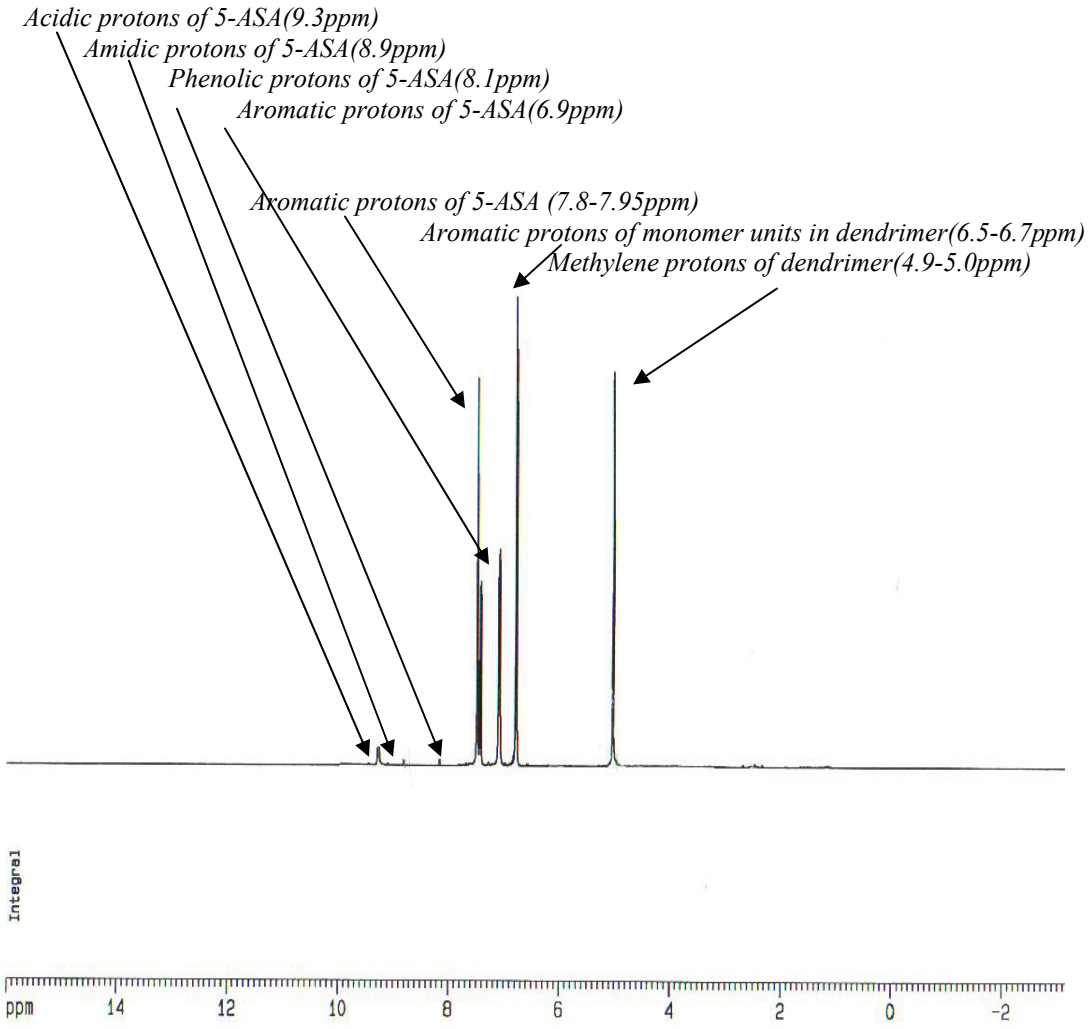



Figure 7. 400MHz $^{1}$H-*NMR spectrum of [G2] – $CH_2OH$ Dendrimer/Mesalamine(5-ASA) conjugate.*

***Conclusions:***

The ability of the dendrimer to form a complex with mesalamine (5-ASA) was explored using aromatic polyether dendrimer as model base polymer.The nature of drug-dendrimer interaction were explored using FT-IR, $^{1}$H-NMR and SEM. Our studies suggest that the aromatic polyether dendrimer may predominantly form a complex with the carboxyl group of mesalamine .this complex is stable in deionized water and methanol. Current studies are exploring the complexation/conjugation ability of these dendrimers to a wide variety of drugs.

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