



## Brief communication

## Poly(amidoamine) dendronized hollow fiber membranes: Synthesis, characterization, and preliminary applications as drug delivery devices

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## ABSTRACT

Poly(amidoamine) (PAMAM) dendrons were prepared from hollow fiber membranes (HFM) consisting of bromomethylated poly(2,6-dimethyl-1,4-phenylene oxide) (BPPO) in a stepwise manner. The prepared HFM were characterized by Fourier transform infrared spectroscopy, elemental analysis, and scanning electron microscopy. The drug loading efficiency and release behavior of the PAMAM dendronized HFM were evaluated using sodium salicylate, sodium methotrexate, and Congo red as model drugs. The results suggest that PAMAM dendronized HFM can be effectively loaded with a variety of drugs and prolong the release of these drugs. The drug loading and release characteristics of the HFM depend on the generation of PAMAM dendrons grafted on the membranes. The prepared PAMAM dendronized BPPO HFM are promising scaffolds in drug delivery and tissue engineering.

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## 1. Introduction

Hollow fiber membranes (HFM) are one of the emerging materials which have been undergoing rapid growth during recent decades. Compared with other types of membrane, HFM are still in their infancy, but have already exhibited several unique features: (1) a large surface mass transfer area; (2) low operating costs; (3) convenience of assembly; (4) flexible filtration modes (“inside out” or “outside in”). Besides applications in separation technology, HFM have been widely used in several biomedical fields, such as blood purification, including hemofiltration, hemodialysis, plasma separation, and blood oxygenation [1], protein separation and purification [2], enzyme immobilization [3], bioreactors [4], artificial organs [5], and drug delivery [6]. Generally, polymers including polysulfone (PS) [7], polyethersulfone (PES) [8], polypropylene (PP) [9], and polyacrylonitrile (PAN) [10] have been used for the fabrication of HFM. The scaffold materials of these HFM are hydrophobic, thus there is a significant potential for the adsorption of proteins onto the membrane surface, resulting in the activation of platelets and leukocytes, and the clotting of hollow fibers [1]. To solve this problem polymers such as polyvinylpyrrolidone (PVP) [1], poly(ethylene glycol) (PEG) [11,12], poly(glycidyl methacrylate) [13,14], poly(acrylonitrile-co-acrylic acid) [15], and

poly(ethylene glycol methyl ether methacrylate) [16] were either blended with, or grafted onto scaffold materials of HFM to improve their hydrophilicity and biocompatibility.

Dendrimers are hyperbranched, monodisperse, and three-dimensional macromolecules with well-defined molecular weights, sizes, and numbers of surface functionalities [17,18]. Poly(amidoamine) (PAMAM) dendrimers, which were first reported by Tomalia in 1985, are the most investigated dendrimers [19,20]. PAMAM dendrimers can be synthesized by Michael addition of amine groups to methyl acrylate, followed by aminolysis of the resulting ester by ethylenediamine to create new reaction sites for further Michael additions. These dendrimers have large numbers of active functional groups, such as hydroxyl, amine, and carboxyl groups, on the dendrimer surface, and thus have excellent aqueous solubility and can be modified with a large number of bioactive molecules [21]. Also, PAMAM dendrimers have numerous relatively non-polar pockets in their interior, which can encapsulate hydrophobic drugs within the dendrimers [22–24]. Although the cytotoxicity of amine-terminated PAMAM dendrimers is a problem, surface modification of these cationic dendrimers by acetylation, PEGylation, or glycosylation can effectively improve their biocompatibility [25]. Based on advances in PAMAM dendrimers, we expected to be able to construct PAMAM dendrimers on the surface of HFM, and that the prepared dendrimer-functionalized HFM would combine the characteristics of HFM (scaffolding material applicability, easily recyclable, a large surface area, and easy assembly into devices) and dendrimers

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(drug delivery systems with easy further modification). However, non-perfect PAMAM structures were obtained because HFM are insoluble in most organic solvents, and reaction between the solid and liquid is incomplete during construction of the dendrimers. Therefore, PAMAM dendronized HFM were prepared instead of dendrimer-functionalized ones. Hyperbranched PAMAM have common features with PAMAM dendrimers because of their similarity in branching, molecular structures, interior cavities, and surface functionalities [26–28]. The high density of amine groups on the membrane surface are expected to load a variety of negatively charged drug molecules, and interior pockets in these hyperbranched PAMAM can encapsulate hydrophobic drugs.

In this study we use bromomethylated poly(2,6-dimethyl-1,4-phenylene oxide) (BPPO) as the scaffold material of HFM. BPPO is a hydrophobic material developed in our group and it has already exhibited several advantages as a scaffold material in the fabrication of membranes, especially HFM [28–32]. BPPO HFM are convenient for further chemical modification and were proved to be biocompatible with several cell lines [6]. As shown in Scheme 1, the bromide groups on BPPO were substituted with amine groups under mild conditions, and the amines were further reacted with methyl acrylate and ethylenediamine to produce PAMAM, as described elsewhere [19,20]. In previous studies PAMAM hyperbranched polymers or dendrimers were grafted on carbon nanotubes [33], mesoporous silica [34], and Fe<sub>3</sub>O<sub>4</sub> nanoparticles [35], however, to the best of our knowledge, this is the first report on the synthesis of dendronized HFM. The drug loading and release behavior of the PAMAM dendronized BPPO HFM were evaluated.

## 2. Materials and methods

### 2.1. Materials

Ethylenediamine, methyl acrylate, and methanol were purchased from Sinopharm Chemical Reagent Co. Ltd (Shanghai, China), and the chemicals were purified by atmospheric distillation before the synthesis of PAMAM dendrons. BPPO HFM were supplied by Tianwei Membrane Co. Ltd (Shandong, China) as a gift. BPPO has a 90% benzyl substitution ratio and 20% aryl substitution

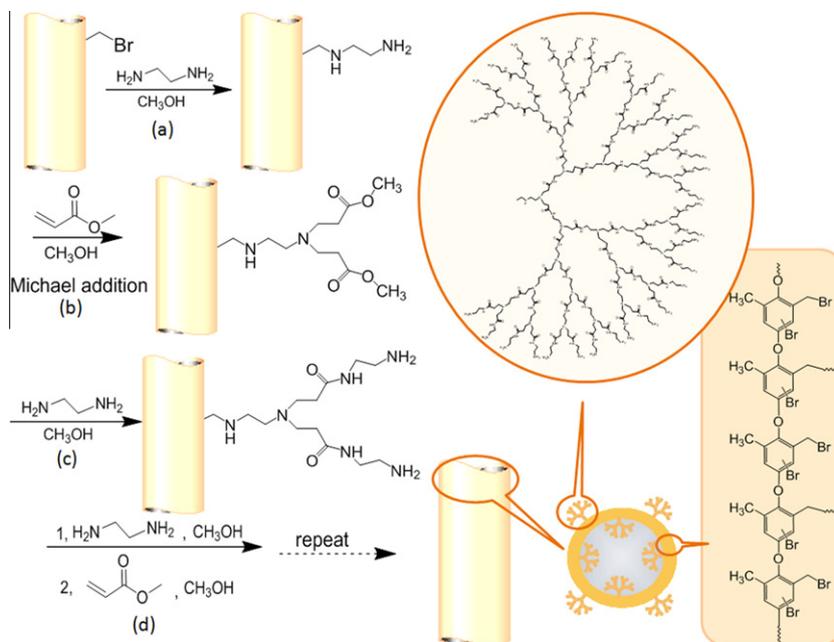
ratio. Sodium salicylate (NaSA) was obtained from Tianjin Damao Chemical Reagent Factory (Tianjin, China). Sodium methotrexate (MTX) and Congo red (CR) were purchased from Sangon Biotech Co. Ltd (Shanghai, China).

### 2.2. Synthesis and characterization of PAMAM dendronized BPPO HFM

BPPO HFM were immersed in ethylenediamine/methanol solution in a three necked round-bottomed flask at 60 °C for 7 days and then washed three times with methanol to obtain the primary amine-functionalized HFM (termed G0 HFM). The G0 HFM obtained were immersed in methanol under a nitrogen atmosphere at room temperature and an excess of methyl acrylate was slowly added. The mixture was stirred for 7 days, followed by three washes of the resulting ester-functionalized HFM (G0.5 HFM) with methanol. The G0.5 HFM obtained were incubated with an excess of ethylenediamine in methanol in an ice bath for 7 days, and the resulting G1 HFM were washed three times with methanol. Higher generation PAMAM dendronized HFM were prepared by repeated Michael addition of amine with methyl acrylate and aminolysis of the resulting ester by ethylenediamine as described above. For G4 and G5 HFM the reaction periods were prolonged from 7 to 14 days. The ideal molecular structures of G0–G5 PAMAM dendronized BPPO HFM are shown in Scheme 2. The products obtained were lyophilized, characterized by Fourier transform infrared spectroscopy (FTIR), elemental analysis, and scanning electron microscopy (SEM), and stored in a dry place before further use.

### 2.3. Drug loading abilities of PAMAM dendronized BPPO HFM

The prepared PAMAM dendronized BPPO HFM, including G3, G4, and G5 HFM, were loaded with three drugs, including NaSA, MTX, and CR, through static adsorption. Lyophilized G3, G4, and G5 HFM were incubated in the drug solutions in Eppendorf tubes at room temperature for 24 h, after which the HFM were removed, and the drug concentrations before and after the loading process were determined using a PGENERAL (UT-1901) UV–vis spectrophotometer (Beijing, China). Wet materials were used for further *in vitro* drug release studies. The concentrations of NaSA, MTX, and CR were determined from the absorbances of the samples at



**Scheme 1.** Synthetic route for PAMAM dendronized BPPO HFM.

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