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Hexanediamine functionalized poly (glycidyl methacrylate-*co*-N-vinylpyrrolidone) particles for bilirubin removal

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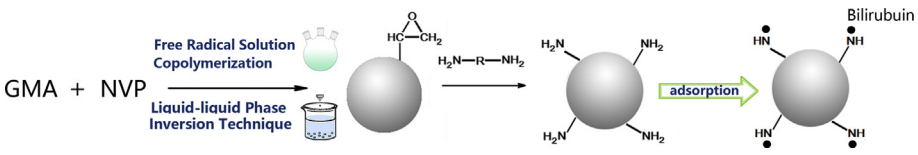
GRAPHICAL ABSTRACT



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ABSTRACT

In this study, we provided a facile method to prepare adsorbents with high content of amino groups for bilirubin removal. Poly (glycidyl methacrylate-*co*-N-vinylpyrrolidone) particle adsorbents were prepared through free radical solution copolymerization followed by a phase inversion technique. Amino groups were further introduced onto the particles by grafting 1,6-hexanediamine molecules. The porosity and specific surface area of the functional particles were 92.9% and 11.8 m^2/g, respectively. Flourier transform infrared spectroscopy and elemental analysis confirmed the successful functionalization of polymeric particles. The cross-linker content and N-vinylpyrrolidone ratios had significant influence on the pore structure of the polymeric particles, as observed by scanning electron microscopy. Batch adsorption experiments were performed to verify bilirubin adsorption behavior of the particles, and a particle column was fabricated to further study the bilirubin removal. The particles exhibited good adsorption capacity of bilirubin without procoagulant activity, and had great potential to be used in hemoperfusion. The study opens a new route to fabricate functional polymer adsorbents.

1. Introduction

Removal of toxins, especially endogenous toxins, is desired for human health. Bilirubin is a serious endogenous toxin, which is a principal degradation product of hemoglobin [1–3]. When the amount of bilirubin in blood increases over 17.1 μmol/L, it can damage nervous system seriously, and is the so-called hyperbilirubinemia [4,5]. The elevated bilirubin interferes with the normal functioning of cellular machinery and eventually manifests systemic toxicity, and may further result in fatal kernicterus [6]. Adsorption is an effective way to remove toxins and has been extensively applied [7–10]. Bilirubin could be removed via electrostatic interaction and/or hydrogen bond interaction by the absorbents containing amino and hydroxyl groups [11–13].

In recent studies, a lot of adsorbents were prepared for bilirubin removal, but there are still some shortages on these adsorbents. For instance, human serum albumin (HSA) immobilized polymeric matrix [14] was used as hemoperfusion column for bilirubin removal from serum, which showed selective adsorption ability for bilirubin. However, the HSA immobilization procedure was complicated, and the used matrix-activating agent (CNBr) in immobilization step was highly toxic. Furthermore, the uncontrolled activity of HSA might also limit the application; and the adsorbent column was expensive. Zong et al. [15] prepared chitosan/amino multiwalled carbon nanotubes (CNTs) composite beads by combining the advantages of chitosan and the nanometer-scale carbon nanotubes; however, the adsorption

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capacity of the adsorbent was as low as 12.7 mg/g. Although the carbon nanotube–chitosan composite beads [16] could reach the adsorption capacity to 40 mg/g by exposing CNTs throughout the open-porous structure of the beads; the physical interaction between the CNTs and chitosan might make the mixture unstable. In this case, the eluted CNTs would cause side effects for human being. Silica hybrids grafted with new guanidine-containing polymers or mesoporous silica particles modified with poly (N-vinyl-2-pyrrolidone) provided good ways to obtain adsorbents with high adsorption capability and stable quality[17,18]; however, the blood compatibility of these silica based adsorbents was unknown. In our previous study, Kevlar/CNT beads were prepared, and showed efficient adsorption ability for bilirubin and acceptable blood compatibility [19] however, the interaction between the Kevlar nanofiber and CNTs was not strong, and the preparation methods of the beads could not be applied in a large scale.

As we know, glycidyl methacrylate (GMA) is often used to introduce functional groups because of its epoxy groups [20–22]. In our early studies, polyethersulfone (PES)-based PGMA particles were prepared for the removal of toxins [23,24]. GMA was *in situ* cross-linking polymerized in PES solution and used to prepare PES-based particles by a phase inversion technique; and then amino groups were grafted onto the particles for the removal of bilirubin [8]. However, we found that the miscibility of PGMA polymers and PES matrix limited the content of functional groups; and thus the bilirubin adsorption amounts of these particles were not prominent. To solve the problems mentioned above, we provide a portal, simple, low-cost method to prepare adsorbents with efficient adsorption ability for bilirubin and good blood compatibility by using poly (vinylpyrrolidone) (PVP).

In this study, GMA and N-vinylpyrrolidone (NVP) were copolymerized by free radical solution polymerization; then the polymer solution was directly prepared into particles by a phase inversion technique. The epoxy groups on the GMA chains offered anchoring sites for further functionalization, and the addition of PVP segments in the copolymers could improve the blood-compatibility [25]. In addition, PVP was also reported to be beneficial to the adsorption property for bilirubin [18]. Then, the particles were modified by 1,6-hexanediamine (HDA) to introduce functional amino groups; and the large amount of amino groups would offer the particle with selective and efficient adsorption ability for bilirubin. The adsorption capacity of bilirubin for these particles was then investigated. Furthermore, the adsorption kinetics and isotherms for bilirubin were studied. As blood contacting materials, the blood compatibility of the particles was also investigated.

2. Material and methods

2.1. Materials

N-vinyl-2-pyrrolidone (NVP) and glycidyl methacrylate (GMA) were obtained from Sigma-Aldrich. N, N′-methylenebisacrylamide (MBA) and azobisisobutyronitrile (AIBN) were received from Aladdin reagent Co. Ltd. (China). N, N-Dimethylacetamide (DMAc) and 1, 6-hexanediamine (HDA) were purchased from Chengdu Kelong Chemical Reagent Co. Ltd. (China) and distilled under reduced pressure before use. Unless otherwise stated, other reagents were obtained from Aladdin and used as received. Deionized (DI) water was used throughout the studies.

2.2. Preparation of poly (glycidyl methacrylate-co-N-vinyl-2-pyrrolidone) copolymers

The copolymerization of GMA and NVP was carried out in DMAc solution. AIBN was used as the initiator and MBA as the cross-linking reagent. A mixture of NVP, GMA, MBA, AIBN and DMAc was placed in a three-necked bottle. After degassing and purging with dry nitrogen gas, the reaction was carried out with vigorous stirring at 500 rpm at 70 °C for 24 h. The contents of NVP of the samples were controlled at 10, 20 and 30 wt.%, respectively; and the polymer solutions were named S-1, S-2 and S-3, respectively. In addition, a controlled sample termed as S-2-0 was prepared without adding the cross-linker MBA. The synthesis conditions for the poly (glycidyl methacrylate-*co*-N-vinyl-2-pyrrolidone) (poly (GMA-NVP)) solutions are shown in Table 1.

2.3. Amination of the particles

Poly (GMA-*co*-NVP) particles were firstly prepared by a modified phase inversion method as described in our earlier report [26]. Briefly, the polymer solutions were dropped into a coagulation bath containing sodium dodecyl sulfate (SDS) aqueous solution to produce porous particles at room temperature. Afterwards, the particles were washed with DI water by changing fresh DI water frequently to remove the residual solvent and unreacted molecules thoroughly. The as-prepared particles were then put into a mixture of water and amino reagent (HDA), and the reaction was carried out at 60 °C for 8 h. Then, the particles were incubated in DI water by changing fresh DI water frequently to remove the unreacted molecules thoroughly. The schematic diagram for preparing the particles is shown in Fig. 1.

2.4. Characterization of the particles

For Fourier transform infrared spectroscopy (FTIR) analysis, the particles were completely dried in an oven at 60 °C for 6 h, and the FTIR spectra were then obtained on a FTIR spectrometer (Nicolet 560, USA) between 500 and 4000 cm^{-1}, using the KBr disk method by grinding and tableting.

A scanning electron microscope (JSM-7500F, JEOL) was used for the morphology observation for the particle samples. The particles were dried in a vacuum oven at room temperature, and then cut with a single-edged razor blade after freezing in liquid nitrogen. Afterwards, the particles were attached to the sample supports and coated with a gold layer.

For particle surface area analysis, the samples were degassed at 100 °C over 24 h. Then, BET-N_2 adsorption/desorption experiments were carried out manometrically at 196 °C using an auto-porosity analyzer (Micromeritics TriStar 3000, USA). The BET surface area was calculated using the BET equation and $p/p_0 = 0.99$ to the adsorption data.

Elemental analysis of the particles was obtained through an Elemental Analyzer (Euro EA 3000). The particles were dried in a vacuum oven at room temperature prior to the test.

The diameter and the porosity of the particles were calculated from the density of the polymer and the particle weight change before and after drying, using the following equations [27]:

$$Diameter = \left(\frac{6[W_A/\rho_P + (W_B - W_A)\rho_W]}{\pi}\right)^{1/3} \quad (1)$$

Table 1
Synthesis conditions of poly (GMA-NVP) polymer solutions.

Sample	Synthesis conditions				
	NVP (g)	GMA (g)	MBA (wt.%)	AIBN (wt.%)	DMAc (g)
S-1	2	18	0.5	0.5	80
S-2	4	16	0.5	0.5	80
S-3	6	14	0.5	0.5	80
S-2-0	4	16	0	0.5	80