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Facile preparation of pH-responsive polyurethane nanocarrier for oral delivery

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ABSTRACT

This study reports a novel one pot synthesis of pH-responsive nanocarrier for oral delivery of hydrophobic drug under gastrointestinal tract. Triblock copolymer MPEG-HTPB-MPEG was synthesized coupling of MPEG and HTPB using hexamethylene diisocyanate(HDI) and pH-responsive carboxylic acid group was attached to polybuthadiene backbone by thiol-ene click reaction in a facile and convenient procedure. The MPEG-HTPB (g-COOH)-MPEG block copolymers were self-organized into micelle assemblies in the water. The size and shape of the micelle assemblies were confirmed by dynamic light scattering (DLS) and transmission electron microscopy (TEM). The nanocarriers have high drug loading ability for poorly water-soluble drug. The pH-responsive profile was demonstrated by pH-dependent swelling and in vitro drug release. <10.0% IBU was released under artificial gastric fluid after 2 h, whereas an immediate release was observed under artificial intestinal fluid. The XTT assay indicated that the micelle obtained from PEG-HTPB (g-COOH)-PEG triblock copolymer are safe in a wide range of concentrations. The results show that pH-responsive PEG-HTPB (g-COOH)-PEG triblock copolymers are promising nanocarriers for the oral administration of hydrophobic drugs.

1. Introduction

Recently polyurethanes have been interesting class of polymers that are applicable in many area including biomaterials synthesis due to their excellent mechanical properties and biocompatibility. In this regard, several biomedical devices such as blood pumps, prosthetic heart, valves and insulation for pacemakers are made from polyurethane [1–3].

Oral delivery under gastrointestinal (GI) tract is one of the most common routes for the administration of drug owing to its relief and reception, particularly in the cases of chronic therapies [4–6]. Despite many advantages, oral formulation of hydrophobic drugs very interesting and challenging subject because drug should be stable and maintained in the active form under the acidic and enzymatic conditions in the GI tract. Upon oral administration of hydrophobic drug owing to low aqueous solubility, high level of P-glycoprotein efflux and poor intestinal permeability, only a fraction of dose is available to systemic circulation for execution of therapeutic response [7]. Polymeric nanoparticles constructed with amphiphilic block polymer with a hydrophilic corona and a hydrophobic core, are particularly attractive for drug carriers. The pH-responsive synthetic amphiphilic polymers can protect the drug against acidic conditions in the stomach (pH < 2.0) and release its cargoes under neutral or basic pH in the small intestine [8–11].

However, design and application of polymeric nanoparticles for oral drug delivery is very difficult because of its undesired release behavior. A good oral carrier must have low burst release in the stomach while time-controlled drug release is another property of oral carriers. After oral administration of drug delivery system 3–16 h is required for its traveling from the mouth to the caecum [12]. So, time-controlled drug release is essential for oral administration. Most designed drug delivery systems for oral application have carboxylic groups in their structure [13–16]. The carboxylic acid groups in pH < 6 are protonated and their solubility decreased while in pH > 6 they are ionized and their solubility were increases [17].

Polyacrylic acid and polymethacrylic acid are the most famous polycaboxylic block in polymer science. These blocks are prepared by controlled polymerizations of tert-butyl acrylate and tert-butyl methacrylic follow-up hydrolysis of tert-butyl groups [18]. In this strategy pH-responsive groups are independent block on structure of block copolymer. Recently, the carboxylic acid functionalized poly(caprolactone) (PCL)-polyethylene glycol(PEG)block copolymer was developed as a new pH-responsive drug delivery system [19,20]. This strategy is very interesting than previous synthetic strategy because the pH-responsive groups are attached to hydrophobic block. Therefore, in the pH < 6, the hydrophobicity of PCL does not change and the self-assembly of nanoparticle is maintained. But in pH > 6, the hydrophobic block convert to hydrophilic block which make disassembly. Despite many advantage, this process has a multi and complex synthetic route. Synthesis of ε-caprolactone monomer functionalized by carboxylic acid is very difficult task.

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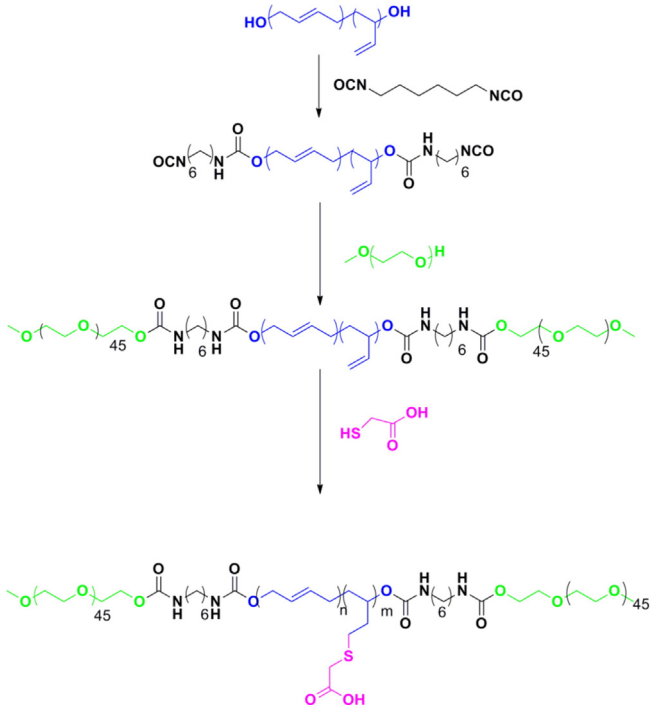

Scheme 1. The synthesis route of pH-responsive of PEG-HTPB (g-COOH)-PEG.

Hydroxyl-terminated polybuthadiene (HTPB) is nonpolar or hydrophobic polymer and it is well known in polymer science. Many researchers have focused on polybuthadiene self-assemble nanostructures. It is reported that polybuthadiene-polyethylene glycol block copolymer (PD-b-PEG) has good tendency for nanostructure formation and it can be successfully loaded by hydrophobic drug [21–24]. Recently Luo et al. reported that the copolymers containing HTPB building blocks with the star architecture is anticipated to have low critical micelle concentration (CMC) in aqueous solution, making for formation of micelles and also HTPB based polymers are useful in drug delivery [25–30] Thus, pH responsive micelle containing polybuthadiene block are yet to be achieved for drug delivery both in oral and intravenous routes. Due to the restricted movement of the molecular segments, the crystallization of the soft/hard phases, and/or the hydrogen bonding interactions between the hard segments PEG-b-HTPB polyurethane copolymers are biodegradable [31].

In the present study, we try to design and develop a simple synthetic route for the synthesis of novel pH-responsive micelles with carboxylic acid groups in hydrophobic segment. Also, we try to investigate capabilities of pH stimuli polybuthadiene based polyurethane micelles assemblies for oral administration of hydrophobic drugs. The pH-responsive micelle comprising of PEG and HTPB was prepared and pH-responsive carbocyclic acid groups were attached to HTPB backbone by click chemistry. These new carboxylic functionalized polybuthadiene block copolymers were self-assembled to pH-responsive micelle in water and the capacity of encapsulation of anti-inflammatory hydrophobic drug such as ibuprofen (IBU) was investigated.

2. Experimental

2.1. Materials

Monomethoxy polyethylene glycol (MPEG) (Mn = 2000, 1000, 5000 g/mol) was purchased from fluka and dried by azeotropic distillation using toluene. Hexamethylene diisocyanate(HDI) was supplied by Merck. HTPB (Mn 3500), containing 15%cis, 25% trans and 60% vinyl was purchased from Chinese Zibo Qilu Chemicals. 2,2-Azobis(isobutyronitrile) (AIBN) (ACROS) was used as received. All solvents were dried under a nitrogen atmosphere prior to use, according to a standard procedure.

2.2. Characterization

NMR spectra were recorded at room temperature in $CDCl_3$ on a Bruker Avance 300-MHz operating at 300.13 MHz. Infrared spectra from 400 to 4000 cm^{-1} were recorded on a Shimadzu 470 FT-IR instrument, using KBr pellets. The absorption spectra were recorded using Perkin-Elmer Lambda 45 UV–visible spectrophotometer. Gel permeation chromatography (GPC) was performed on Agilent Tech., Model 1260 infinity equipped with differential refractometer and MIXED column. Tetrahydrofuran (1.0 mL/min) was used as eluent at 30 ± 1 °C. The calibration of column was performed with narrow polydispersity polystyrene standards (Fluka). To fit the log10M vs. time calibration curve, a third-order polynominal was applied and a linear correlation was found in the molecular range 2×10^2–2×10^6. TEM image of nanoparticles were recorded using a Philips CM-30 with accelerating voltages of 150 and 250 kV instrument by drop casting the sample on Formvar-coated copper grid.

Dynamic light scattering (DLS) was performed using a Nano-ZS ZEN3600 device using 633 nm red laser (at 90° angle) from Malvern Instruments. At 90° scattered fluctuations were detected to generate correlation function [$g^2(t)$], from this function diffusion coefficient(D) calculated by utilizing Cumulant method. Particle diameter was calculated by applying stock-Einstein equation. Three times independent

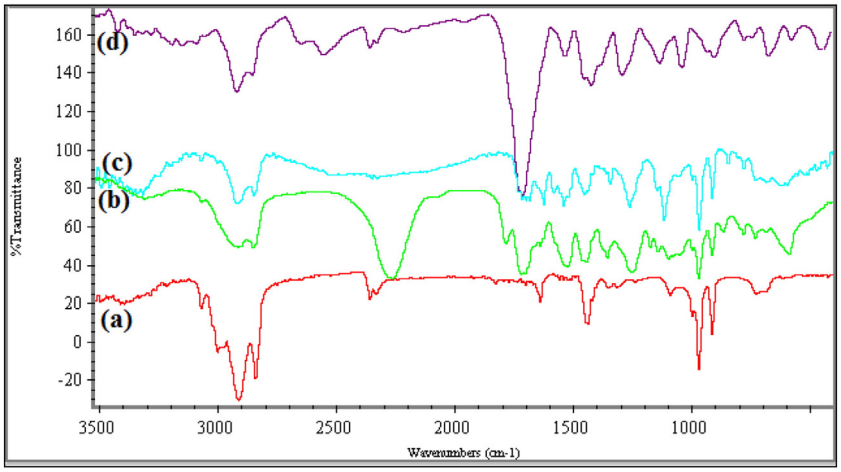

Fig. 1. FTIR spectra of HTPB (a), NCO-HTPB-NCO (b), PEG-HTPB-PEG (c) and PEG-HTPB (g-COOH)-PEG (d).