



改性聚醚砜微球在高胆红素血症中的应用研究*

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【摘要】目的 设计并制备一种具有良好机械性能和生物相容性的高效率胆红素吸附剂。**方法** 设计合成吡啶季铵盐, 随后通过相转化法和静电喷雾技术制备改性聚醚砜微球PES/p(4-VP-co-N-VP)@6。通过核磁共振谱图、扫描电镜等测试手段研究聚合物组分及微球的形貌, 测试微球的基本性能, 以及胆红素的吸附效率, 并深入探究其吸附机制。同时对微球的血细胞计数和凝血时间进行测试。**结果** 制备的改性聚醚砜微球直径约为700~800 μm。与原始PES微球相比, PES/p(4-VP-co-N-VP)@6的表面和内部结构并无明显变化, 同样具备疏松多孔结构, 除却不规则大孔外还散在分布一些微孔。与对照PES组相比, 改性后的微球在胆红素PBS缓冲溶液中静态吸附180 min后胆红素清除效果为(94.91±0.73)%, 差异有统计学意义($P<0.0001$)。凝血时间检测中, 空白血浆组、对照PES组及改性PES微球组的活化部分凝血活酶时间(activated partial thromboplastin time, APTT)分别为(27.57±1.25) s、(28.47±0.45) s及(30.4±0.872) s, 实验组与其余两组差异均有统计学意义($P<0.01$, $P<0.05$)。红细胞、白细胞计数无明显改变。**结论** 制备的微球具有高效胆红素吸附性能、优异力学性能和热稳定性, 以及良好血液相容性, 有望应用于肝衰竭患者的临床治疗。

【关键词】 高胆红素血症 吡啶季铵盐 改性聚醚砜微球 胆红素吸附剂 血液灌流

Application of Modified Polyether Sulfone Microspheres in Hyperbilirubinemia DENG Ningyue, JIN Lunqiang, SU Baihai[△]. Department of Nephrology, West China Hospital, Sichuan University, Chengdu 610041, China

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【Abstract】 Objective To design and prepare a high efficiency bilirubin adsorbent with good mechanical properties and biocompatibility. **Methods** In this study, quaternary ammonium pyridine was designed and synthesized, and then modified polyether sulfone microspheres, or PES/p(4-VP-co-N-VP)@6 microspheres, were prepared by phase conversion and electrostatic spraying. The morphology of the polymer components and the microspheres were studied by means of nuclear magnetic resonance (NMR) spectroscopy and scanning electron microscopy. The basic properties of the microspheres and their bilirubin adsorption efficiency were tested, and the adsorption mechanism was further explored. Blood cell counts and the clotting time of the microspheres were also measured. **Results** The diameter of the modified polyether sulfone microspheres prepared in the study was approximately 700-800 μm. Compared with the original PES microspheres, the surface and internal structure of PES/p(4-VP-co-N-VP)@6 microspheres did not change significantly, and they also had a loose porous structure, with some micropores scattered around in addition to irregular large pores. Compared with the control group, the bilirubin removal effect of the modified microspheres was (94.91±0.73)% after static adsorption in bilirubin PBS buffer solution for 180 min, with the difference being statistically significant ($P<0.0001$). According to the findings for the clotting time, the activated partial thromboplastin time (APTT) of the blank plasma group, the control PES group, and the modified PES microsphere group were (27.57±1.25) s, (28.47±0.45) s, and (30.4±0.872) s, respectively, and the difference between the experimental group and the other two groups was statistically significant ($P<0.01$, $P<0.05$). There was no significant change in red blood cell and white blood cell counts. **Conclusion** The microspheres prepared in the study have high efficiency in bilirubin adsorption, excellent mechanical properties and thermal stability, and good blood biocompatibility, and are expected to be used in the clinical treatment of patients with liver failure.

【Key words】 Hyperbilirubinemia Pyridine quaternary ammonium salt Modified polyether sulfone microspheres Bilirubin adsorbent Hemoperfusion

胆红素是红细胞分解产生的一种疏水性产物^[1-2]。在正常人的血液中, 常以直接胆红素和间接胆红素两种形式

存在。直接胆红素通过肝脏与葡萄糖醛酸或其他物质结合, 而间接胆红素主要与白蛋白结合^[3]。胆红素在血液中的过度积累可引起高胆红素血症, 从而导致黄疸和组织细胞坏死, 进一步引发急性肝衰竭, 胆红素还可以通过生物膜扩散到大脑和各种组织^[4-8]。高胆红素血症是一种临床难治性疾病。血液中过量的胆红素会对人体细胞、组织和器官造成损伤, 导致严重的后遗症, 甚至引发死亡^[9-11]。

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血液灌流可有效去除胆红素,从而治疗高胆红素血症^[12-13],胆红素清除效率是评估血液灌流效果的重要指标^[14-15]。

目前临床主要使用的是双重血浆分子吸附系统,用中性大孔树脂和离子交换树脂两种吸附剂相联合进行血浆吸附治疗。据临床数据统计,治疗后总胆红素浓度仅下降约40%,且有一定程度的血细胞数目改变^[16]。活性炭^[17]、石墨烯^[18]、分子印迹材料^[19]等也被用于胆红素吸附,然而,多数材料面临着难以解决的问题,如易脱落、吸附性能低、血液相容性差等^[6, 20-21]。当前研究的具有特定结合位点的新型多孔材料,如金属有机框架^[22-24]、多孔芳香框架^[25]等,虽然大大提升了胆红素吸附性能,但也在制备复杂,安全性不明等问题。

季铵盐是由阴阳离子组成的,能够通过电荷作用,吸附带负电荷的物质,从而吸引或清除目标^[26]。吡啶是一

种含氮六元杂环,其中氮原子所带的孤对电子可与溴代烷烃发生取代反应构建季铵盐,经过改性的聚4-乙烯基吡啶及其共聚物在吸附^[27]、离子交换^[28]、抗菌材料、树脂交换膜^[29]等领域均有广泛应用。吡啶季铵盐的正电荷和吡啶环的大 π 键可与胆红素分子产生静电作用和 π - π 共轭作用^[8, 25, 30],从而提升吸附性能。

本文通过一锅法聚合并取代,构建吡啶季铵盐正电荷聚合物,再经过简便的共混静电喷雾法和相转化技术制备了带有正电荷、疏松多孔的改性聚醚砜微球PES/p(4-VP-co-N-VP)@6(图1)。由于静电作用和分子间作用力,PES/p(4-VP-co-N-VP)@6表现出良好的胆红素吸附性能,经过热重分析、应力应变实验检验微球的热稳定性和机械性能,采用血常规和凝血时间实验初步评估了微球的血液相容性。现报告如下。

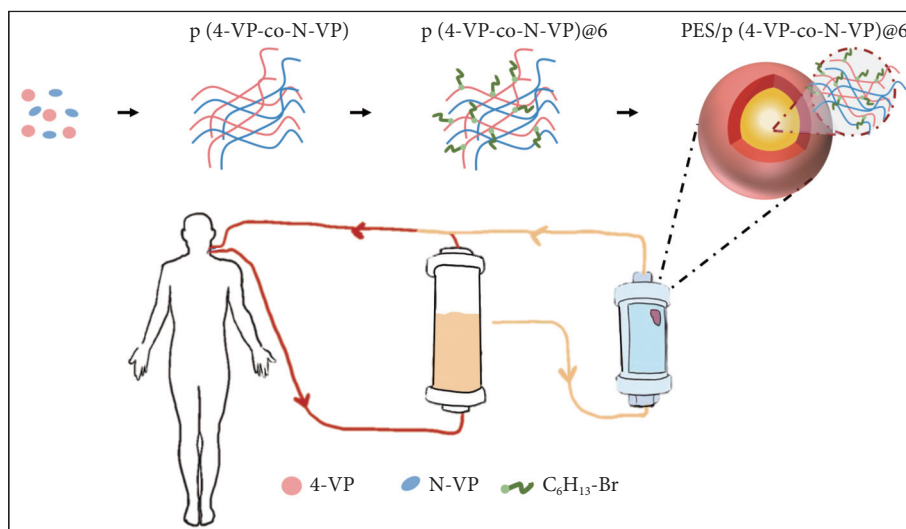


图1 PES/p(4-VP-co-N-VP)@6微球制备及应用示意图

Fig 1 Schematic diagram of the preparation and application of PES/p(4-VP-co-N-VP)@6 microspheres

4-VP: 4-vinyl pyridine; N-VP: N-vinyl-2-pyrrolidinone.

1 材料与方法

1.1 材料及仪器

1.1.1 材料

聚醚砜(polyethersulfone, PES, Ultrason E6020P)购自德国巴斯夫公司;胆红素(98%)、4-乙烯基吡啶(4-vinylpyridine, 4-VP, 96%)和氢氧化钠(NaOH, AR, 96%)购自上海阿拉丁生化科技股份有限公司;溴己烷(99%)、偶氮二异丁腈(AIBN, 98%)和N-乙烯基吡咯烷酮(N-vinyl-2-pyrrolidone, N-VP, 90%)购自上海阿达玛斯试剂有限公司;N,N-二甲基乙酰胺(DMAc, AR, 99%)和N,N-二甲基甲酰胺(DMF, AR, 99.5%)购自中国成都科隆公司。在整个研究过程中使用去离子水(DI水)。

1.1.2 仪器

核磁共振波谱仪(AV III HD 400 MHz, Bruker, 德国),扫描电子显微镜(Phenom Pure电子显微镜, Thermo Scientific公司, 荷兰),伺服拉力试验机(HZ-1004A, 中国),热重分析仪(METTLER TOLEDO TGA/DSC 3+, 瑞士),酶标仪(SpectraMax®ABS Plus, 美国),全自动血液细胞分析仪(BC-5100, 迈瑞生物医疗电子有限公司, 中国深圳),全自动血液凝固分析仪(Sysmex CA-500, 日本)。

1.2 吡啶季铵盐的制备与表征

将2 g 4-VP和445 mg N-VP溶解于15 mL DMAc中,加入51 mg AIBN,室温下氮气吹扫、磁力搅拌30 min使其分散均匀,抽真空后氮气保护下于80 °C反应24 h,此时即可反应生成p(4-VP-co-N-VP)。继续加入4 g溴代正己烷于

反应溶液中, 继续于80 ℃反应24 h, 此时溶液为棕色, 反应结束后, 将溶液加入丙酮中, 有浅棕色固体析出, 过滤后真空干燥处理, 即得到聚合物p(4-VP-co-N-VP)@6, 密封保存备用。

1.3 改性聚醚砜微球的制备

称取一定质量的PES粉末和聚合物p(4-VP-co-N-VP)@6溶于DMAc中, 配制两种纺丝溶液, 具体组分如表1所示。完全溶解后, 吸取适量溶液通过液-液相转化方法和静电喷雾技术制备出大小均匀的两种微球[PES和PES/p(4-VP-co-N-VP)@6], 将微球置于去离子水中, 间隔24 h更换一次去离子水, 以去除残留的溶剂。

表1 纺丝溶液组分
Table 1 The components of spinning solutions

Solution	PES	p(4-VP-co-N-VP)@6	DMAc
PES	12%	0	88%
PES/p(4-VP-co-N-VP)@6	12%	8%	80%

1.4 改性聚醚砜微球的性能测试与结构表征

通过扫描电子显微镜(SEM)观察了聚醚砜微球的表面和截面形貌, 将微球冻干处理, 经液氮急冻后切开, 将样品用离子溅射法(真空度8 kPa, 电流6~8 mA)在表面喷涂金, 用于观测。然后, 利用能量色散X射线能谱对所选零件部位的SEM图像进行元素组成和分布分析。

微球的力学性能通过应力实验测定。抗压强度测试使用配备10 kg传感器的通用试验机, 压缩率设为10 mm/min, 试验极限应变为70%。

微球的热稳定性通过热重分析仪测定。测试前将聚醚砜微球在60 ℃的烘箱中干燥24 h, 称取4~10 mg干燥后的微球, 加入至坩埚中。热重分析(thermogravimetric analysis, TGA)曲线由热重分析仪获得, 并根据TGA数据导出了导数热重(derivative thermogravimetric, DTG)曲线。加热程序设定为50 ℃恒温平衡30 min, 然后以10 ℃/min的加热速率从50 ℃加热到800 ℃, 整个试验在N₂气氛下进行。

1.5 胆红素的吸附测试

由于胆红素易见光分解, 所有实验操作皆在避光条件下进行。

1.5.1 吸附动力学

称取10 mg胆红素, 以1.25 mL 0.1 mol/L NaOH溶液室温下溶解, 再加入pH7.4的磷酸盐缓冲溶液定容至50 mL, 混合均匀, 避光保存。

称取200 mg PES或PES/p(4-VP-co-N-VP)@6微球, 加入8 mL胆红素缓冲溶液中, 在37 ℃环境下, 120 r/min恒

温震荡, 以在相同环境下恒温震荡的无球胆红素缓冲溶液作为空白对照组, 分别于0 min、15 min、30 min、60 min、120 min、180 min吸取100 μL溶液, 利用酶标仪检测波长为438 nm处的吸光度(A₄₃₈)。每组样品重复3组平行。

微球的胆红素吸附率可由式(1)计算:

$$R = \frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}} \times 100\% \quad (1)$$

式(1)中, R 为吸附率; A_{control} 和 A_{sample} 为空白组和实验组的胆红素缓冲溶液的吸光度。

为深入探究吸附机理, 采用拟一级和拟二级动力学模型分析了胆红素吸附动力学过程。拟一级方程, 又称Lagergren速率方程, 是液固体系吸附的一阶方程, 拟二级方程是基于吸附速率受化学吸附原理调控的假设。计算公式如式(2)、(3)^[31-32]所示:

$$\ln(q_e - q_t) = \ln q_e - k_1 t \quad (2)$$

$$\frac{t}{q_t} = \frac{1}{k_2 q_e^2} + \frac{t}{q_e} \quad (3)$$

其中 q_e 和 q_t 分别为计算的吸附平衡时的吸附量和时刻吸附量, t 是吸附时间, k_1 和 k_2 分别为拟一级和拟二级动力学模型的吸附速率常数。

1.5.2 不同初始浓度的静态胆红素吸附

称取一定质量胆红素, 以0.1 mol/L NaOH溶液室温下溶解, 再加入一定体积pH=7.4的磷酸盐缓冲溶液, 配制质量浓度分别为100 mg/L、200 mg/L、300 mg/L、400 mg/L和500 mg/L的胆红素缓冲溶液, 混合均匀后避光保存。

称取100 mg PES或PES/p(4-VP-co-N-VP)@6, 加入8 mL胆红素缓冲溶液中, 在37 ℃环境下, 120 r/min恒温震荡, 以在相同环境下恒温震荡的无球胆红素缓冲溶液作为空白对照组, 于180 min吸取100 μL溶液, 利用酶标仪检测波长为438 nm处的吸光度。每组样品重复3组平行。

按式(1)计算聚醚砜微球的胆红素吸附率。

1.6 血液相容性

健康人新鲜血液(来自1名24岁男性献血者)使用含有枸橼酸钠(用于凝血时间试验, 抗凝血比为1:9)或乙二胺四乙酸(用于评估血细胞计数)作为抗凝血剂的真空管(5 mL, 江苏康健公司, 中国)收集。本实验由四川大学华西医院批准进行, 所有实验均按照相关法律和国家指南(GB/T 16886.4-2003/ISO 10993-4:2002, 中华人民共和国国家质量监督检验检疫总局, 中华人民共和国国家标准化委员会)进行。任何以人体为实验对象的实验均获得知情同意, 并得到了四川大学华西医院医学伦理委员会的批准(批准号2024553), 使用人体血液符合所有规定。

1.6.1 血细胞计数

采用血细胞计数法研究微球对血细胞的影响。将适量微球浸没在100 μL 生理盐水中浸泡过夜。去除生理盐水后,注入新鲜全血100 μL ,在37 $^{\circ}\text{C}$ 环境下孵育30 min,然后去除微球,收集剩余血液采用全自动血液细胞分析仪测定血细胞计数。将无球新鲜全血作为空白对照,每个样品重复3组平行。

1.6.2 凝血时间检测

活化部分凝血活酶时间(activated partial thromboplastin time, APTT)、凝血酶原时间(prothrombin time, PT)和凝血酶时间(thrombin time, TT)检测试剂购自SIEMENS公司,检测前均预热至37 $^{\circ}\text{C}$ 。新鲜血液(枸橼酸钠抗凝)4 000 r/min离心15 min得到乏血小板血浆(platelet poor plasma, PPP),取适量微球,加入300 μL PPP浸泡,于37 $^{\circ}\text{C}$ 环境下,孵育30 min。无球PPP为空白对照组。使用全自动凝血仪测定APTT、PT、TT。每个样品重复3组平行。

1.7 统计学方法

每个实验独立进行,至少进行3次定量分析。结果以 $\bar{x} \pm s$ 表示。两组采用 t 检验分析,多组采用单因素方差分析,并用Tukey事后检验进行组别间的分析。 $P < 0.05$ 为差异有统计学意义。

2 结果与讨论

2.1 聚合物表征

以氘代二甲基亚砜作为溶剂,原料4-VP、N-VP及聚合物p(4-VP-co-N-VP)@6的 ^1H NMR谱图如图2所示。对比单体(4-VP、N-VP)的核磁氢谱图,聚合物p(4-VP-co-N-VP)@6在 $5 \times 10^{-6} \sim 7 \times 10^{-6}$ 的双键上的质子峰消失,提示聚合成功。 $0.5 \times 10^{-6} \sim 2 \times 10^{-6}$ 新增的质子峰位为取代烷基基上的氢,提示取代成功。以上结果表明,p(4-VP-co-N-VP)@6制备成功。

2.2 聚醚砜微球的表征及性能

SEM观察(图3A)发现,聚醚砜微球直径约为700 ~ 800 μm 。与原始PES微球相比,PES/p(4-VP-co-N-VP)@6的表面和内部结构并无明显变化,同样具备疏松多孔结构,除却不规则大孔外还散在分布一些微孔。然后用EDS元素图对改性聚醚砜微球的化学元素进行分析。结果(图3B)表明,C、N、O、S、Br等元素均匀分布在PES/p(4-VP-co-N-VP)@6表面。以上结果表明,成功制备了吡啶季铵盐吸附微球。

微球的应力-应变曲线如图4A和图4B所示,PES和PES/p(4-VP-co-N-VP)@6的压缩模量无明显差异,均表现

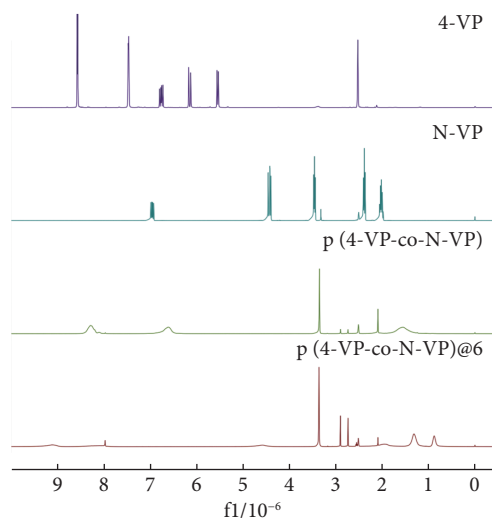


图2 4-VP、N-VP、p(4-VP-co-N-VP)和p(4-VP-co-N-VP)@6的核磁共振氢谱图

Fig 2 The ^1H NMR spectra of 4-VP, N-VP, p(4-VP-co-N-VP), and p(4-VP-co-N-VP)@6

4-VP: 4-vinyl pyridine; N-VP: N-vinyl-2-pyrrolidinone.

出良好的机械强度。在血液灌流中,吸附剂应能承受100 ~ 500 mmHg (13.3 ~ 66.7 kPa)的血液动压。在66.7 kPa的压力下,PES/p(4-VP-co-N-VP)@6的应变仅为10.2%,表明PES/p(4-VP-co-N-VP)@6能够承受血液灌流中的压力。利用热重分析仪对微球的热稳定性进行了研究,其TGA曲线和推导获得的曲线如图4C和图4D。在200 $^{\circ}\text{C}$ 前,微球质量保持相对稳定,表明微球在室温等血液灌流或运输保存条件下具有良好的热稳定性。

总体而言,PES/p(4-VP-co-N-VP)@6具有多孔结构,和良好的热稳定性及机械性能,可用作血液灌流吸附剂使用。

2.3 聚醚砜微球对胆红素的吸附能力

如图5A所示,随着胆红素初始浓度的增加,PES/p(4-VP-co-N-VP)@6对其的吸附率并无明显改变,始终维持在95%以上。PES的吸附率波动在10% ~ 20%。结果表明,PES/p(4-VP-co-N-VP)@6具有很好的吸附潜力,具备成为高胆红素血症患者的高效吸附剂的可能。

微球对胆红素吸附率随时间的变化如图5B所示,在前30 min内,PES/p(4-VP-co-N-VP)@6对胆红素的吸附率迅速增加,随后吸附速率逐渐减慢,120 min至180 min逐渐趋于平衡,吸附量接近95%。而PES对胆红素的吸附率变化缓慢,180 min时吸附率仅有 $(23.75 \pm 1.86)\%$ 。PES/p(4-VP-co-N-VP)@6对胆红素的吸附优势可能因为季铵盐正电荷的电荷作用以及氢键的共同作用,另外疏松多孔的结构特征也有利于微球对胆红素的充分吸附。

拟合模型的参数如表2所示,PES/p(4-VP-co-N-

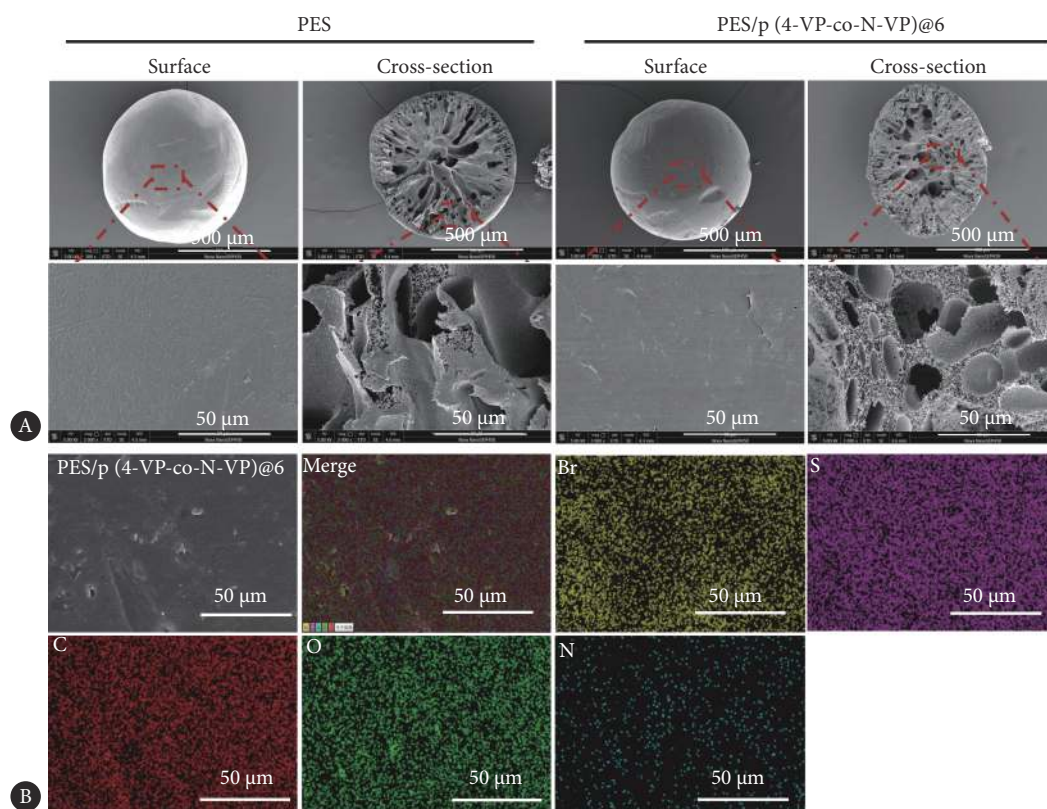


图3 PES和PES/p(4-VP-co-N-VP)@6的形貌和化学成分

Fig 3 Morphology and chemical composition of PES and PES/p(4-VP-co-N-VP)@6

A, SEM images of the surface and cross section of the microspheres; B, energy spectrum of the microspheres.

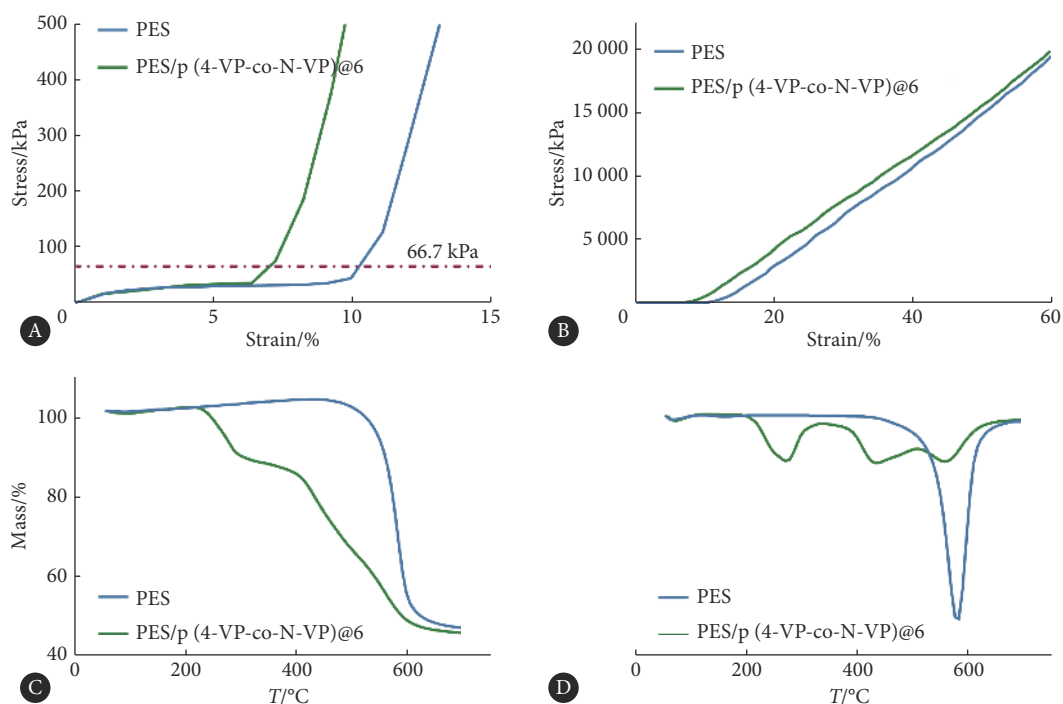


图4 PES和PES/p(4-VP-co-N-VP)@6的力学性能和热稳定性

Fig 4 Mechanical properties and thermal stability of PES and PES/p(4-VP-co-N-VP)@6

A and B, Typical compressive stress-strain curves of the microspheres, A is a local amplification of B. C, The thermogravimetric analysis curves of the microspheres. D, The derivative thermogravimetric curves of the microspheres.

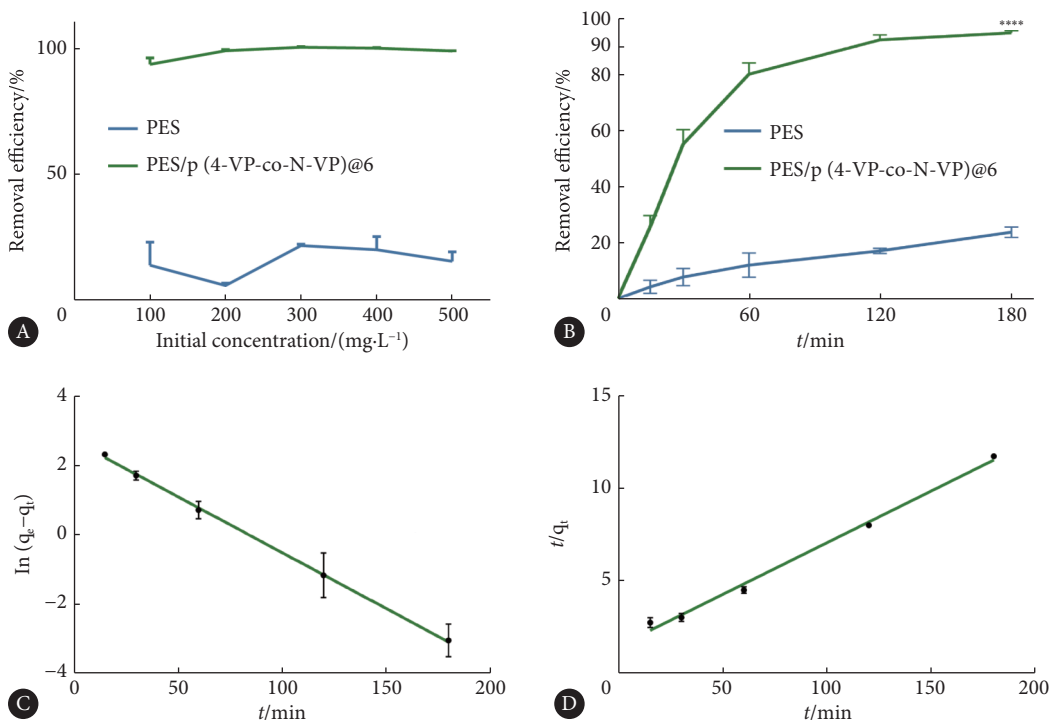


图 5 聚醚砜微球对胆红素的体外吸附效果

Fig 5 Bilirubin adsorption *in vitro*

A, Adsorption ability of the microspheres at different initial concentrations ($T=37\text{ }^{\circ}\text{C}$, $t=3\text{ h}$), $n=3$. B, Bilirubin adsorption kinetics of the microspheres ($T=37\text{ }^{\circ}\text{C}$, initial bilirubin=200 mg/L), $n=3$, **** $P<0.0001$. C, The pseudo-first-order equation of PES/p(4-VP-co-N-VP)@6, $n=3$. D, The pseudo-second-order equation of PES/p(4-VP-co-N-VP)@6, $n=3$.

VP)@6对胆红素的吸附速率常数 r_1^2 为0.9742, r_2^2 为0.9917 (图5C和图5D),由此可见,其吸附机理与拟二级动力学模型更加吻合,表明可能吸附机制为胆红素分子的负电荷与季铵盐部分的正电荷产生电荷作用,并且胆红素中的羧基、胺基基团与吸附剂中的羟基、羧基等也可形成氢键,双重化学作用促使吸附。

2.4 血液相容性

通过血细胞计数和凝血时间实验评价了微球的血液相容性。血细胞计数是评价生物材料血液相容性的基础。接触微球后的血细胞计数和体积分布结果如图6A和图6C所示。与PES/p(4-VP-co-N-VP)@6孵化前后,全血中的红细胞和白细胞的数量和体积分布均无明显变化,血小板虽有轻微下降,但依然在正常参考范围内,考虑可能是少量血小板在微球表面黏附、活化,故而血液中略微减少。

为了研究PES/p(4-VP-co-N-VP)@6对凝血系统的影响,本研究测量了微球孵育后的血浆的APTT、PT和TT,数据如图6B所示。PES/p(4-VP-co-N-VP)@6对APTT [(30.4±0.87) s]有延长作用,但与PPP相比,PT和TT并无明显变化。凝血时间的改变可能与具有高亲水性的N-VP组分相关,提高亲水性可减少材料表面蛋白的黏附,从而降低凝血级联反应激活的风险^[33]。

2.5 结论

本研究通过聚合取代的方法成功构建了带有正电荷的吡啶季铵盐聚合物,并通过相转化法和静电喷雾技术制备改性的聚醚砜微球PES/p(4-VP-co-N-VP)@6。该微球具有优异的力学性能及热稳定性,通过电荷作用和分子间作用力使得其对于胆红素具有突出的吸附性能,增加亲水性的改性方案赋予微球良好的血液相容性。综上所述,PES/p(4-VP-co-N-VP)@6微球为未来肝衰竭患者的

表 2 聚醚砜微球胆红素吸附的拟一级和拟二级动力学方程的参数

Sample	$q_{e(\text{exp})}/(\text{mg/g})$	Pseudo-first-order equation			Pseudo-second-order equation		
		$k_1/(\text{g/mg}\cdot\text{min})$	$q_{e(\text{cal})}/(\text{mg/g})$	r_1^2	$k_2/(\text{g/mg}\cdot\text{min})$	$q_{e(\text{cal})}/(\text{mg/g})$	r_2^2
PES/p(4-VP-co-N-VP)@6	15.39	0.03215	14.67	0.9742	2.073×10^3	18.00	0.9917

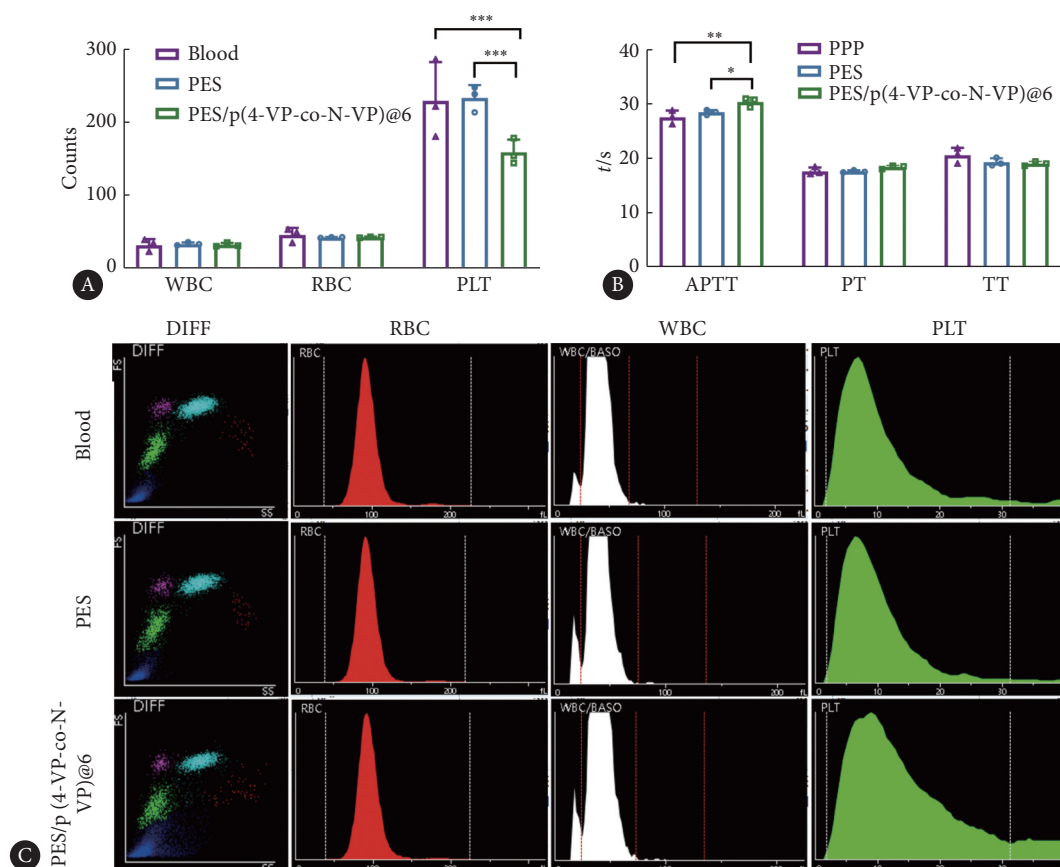


图6 微球体外血液相容性的评估

Fig 6 Evaluation of the biocompatibility of microspheres *in vitro*

RBC: red blood cells; WBC: white blood cells; PLT: platelets; DIFF: differential white blood cell count. A, Cell counts of RBC ($\times 10^{11} \text{ L}^{-1}$), WBC ($\times 10^8 \text{ L}^{-1}$) and PLT ($\times 10^9 \text{ L}^{-1}$) after coculturing with microspheres for 30 min ($n=3$), *** $P<0.001$. B, Clotting times of PPP after coculturing with microspheres for 30 min ($n=3$), * $P<0.05$, ** $P<0.01$. C, DIFF scatter diagram and histograms of RBC, WBC and PLT after coculturing with microspheres for 30 min.

临床治疗提供了新的思路与策略,具有很大的应用前景。

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Author Contribution DENG Ningyue is responsible for conceptualization, data curation, formal analysis, investigation, validation, and writing--original draft. JIN Lunqiang is responsible for conceptualization, funding acquisition, investigation, methodology, and validation. SU Baihai is responsible for conceptualization, funding acquisition, resources, supervision, and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

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Declaration of Conflicting Interests All authors declare no competing interests.

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